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TRYPANOCIDAL AND ANTI-MALARIAL DRUGS.

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(Wellcome Chemical Research Laboratories, London.)

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It is a counsel of perfection, which not even the most enthusiastic of organic chemists would urge, to ask medical men to use the systematic, chemical names by which synthetic drugs are described in purely chemical literature. Chemists themselves find these names impossible for daily laboratory use and almost invariably substitute for them such simple designations as a letter, or a name, with a serial number, *e.g.*, B.117 or Galen 45, and new drugs are even submitted for biological tests and clinical trials under these laboratory abbreviations. When the results of such tests are promising the new drug is usually patented and the patentee generally takes the further protective step of registering for it a trade-mark name. When in due course the patent lapses the manufacture of the drug may be taken up by other people, each of whom may register for it a new trade-mark name for the protection of his particular brand of the product. Should the drug be admitted to the Pharmacopoeia or the British Pharmaceutical Codex, the authorities for these publications will coin a new name, which is non-proprietary and available for general use. In these and other ways the present complex synonymy has been built up. The present authors have compiled a list of 21 names, coined by official and unofficial efforts in various countries, for the drug known officially in this country and the United States as neoarsphenamine. Glossaries of such names are printed from time to time in pharmaceutical publications, but as a rule these are confined to well-established drugs and perforce cannot include names of drugs which are still in the experimental stage.

It is not practicable to prepare a complete guide to names of drugs which have been tried in malaria and trypanosomiasis, and to which reference may have been made in the literature of these two diseases; in the following paragraphs mention is made only of drugs referred to in reviews, which have appeared in the last 10 years in this *Bulletin*, and which in the authors' experience are frequently the subject of enquiry. It should be understood that many of the names given are trade-marks, and that though the essential component may be the same in different brands of a drug, it does not necessarily follow that all

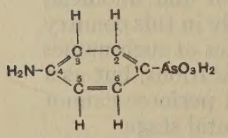
the brands are identical; they may differ in the base associated with an acid or *vice versa*, in the amount of water of crystallization present, in physical condition and in other ways, all of which may influence a physician's choice among them. The systematic chemical names used and the numbering of the positions of substituents in the formulae are based on the rules adopted in the *Journal of the Chemical Society of Great Britain*. The references given are to this *Bulletin* unless stated otherwise.

Quinquevalent (*Pentavalent*) *Arsenic Compounds*.—The first arsenical drug used in the treatment of trypanosomiasis was 4-aminophenylarsonic acid (formula I) generally used in the form of the sodium salt and for which the following names are in use :—sodium aminarsonate (B.P.C.), sodium arsanilate, arsamin, atoxyl, soamin, trypoxyl (1932, **29,** 642).

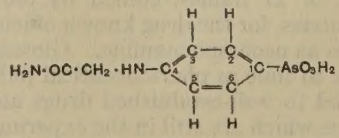
An interesting derivative of this substance is 4-phenylglycylamidearsonic acid (formula II), for which the systematic name *N*-phenylglycineamide-*p*-arsonic acid (B.P.C.) is also sometimes used. In the form of its sodium salt this product is known as tryparsamide, other names being tryparsone (B.P.C.), glyphénarsine (1934, **31,** 578 : Pharm. Belg. iv), tryponarsyl (1928, **25,** 790 ; 1934, **31,** 578), trypotan (1933, **30,** 786) and novatoxyl (1930, **27,** 230).

Other products derived from the same primary substance are 4-hydroxyethylaminophenylarsonic acid (etharsanol) and 4-hydroxypropylaminophenylarsonic acid (proparsanol), also both used as sodium salts (1929, **26,** 199). With a hydroxyl group substituted in position 2 and acetylation of the amino- group, the primary product becomes 2-hydroxy-4-acetylaminophenylarsonic acid, the sodium salt of which is Fourneau 270 (orsanine ; 1932, **29,** 640).

In a second series the position of the amino- group in relation to the arsonic acid residue is changed from 4 to 3. The best known member of this group is 4-hydroxy-3-acetylaminophenylarsonic acid (formula III), the diethylamine salt of which is acetylarsan (1927, **24,** 569) and the quinine salt quiniostovarsol, whilst the sodium salt is known under the names acetarsol (B.P.C.), acetarsone, kharophen, orarsan, osvarsan (1931, **28,** 1010), spirocid and stovarsol. A variant, in which the acetyl group, $CH_3.CO.$, is replaced by the formyl radical, is 3-formylamino-4-hydroxyphenylarsonic acid, the sodium salt of which has the names formyphénarsine (Pharm. Belg. iv) and tréparsol (1931, **28,** 907).



(I)



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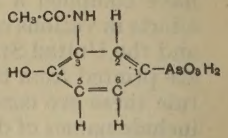
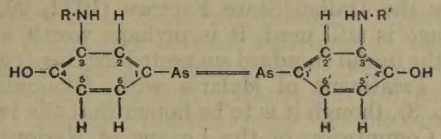


(III)

An isomeride of stovarsol, in which the relative positions of the acetylamino- and hydroxyl groups have been changed, is 2-hydroxy-5-acetylaminophenylarsonic acid, the sodium salt of which is troposan and the quinine salt quinine-troposan (1929, **26,** 380).

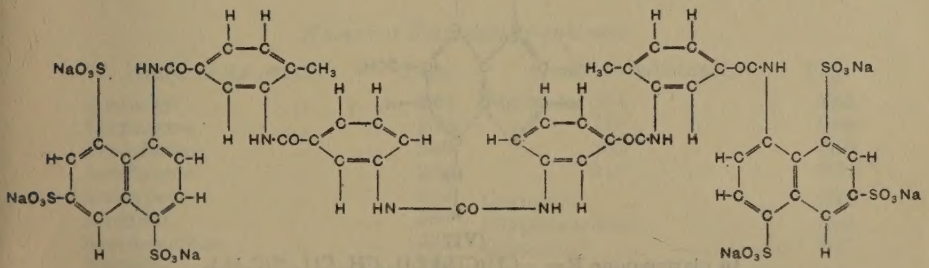
Tervalent (*Trivalent*) *Arsenic Compounds*.—The best known of these is 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene dihydrochloride, commonly known as salvarsan or 606, but for which the non-proprietary

name arsphenamine is in common use in the British Empire and the United States. The drug is now generally used in the form of one of its two principal derivatives. The first of these is the *N*-methylene-sulphoxylate (formula IVa), which is neoarsphenamine (B.P.), other names being neoarsenphenolamine, neoarsaminol, neokharsivan, neosalvarsan (Ehrlich 914), novarsan, novarsenobenzene, novarsenobenzol, novarsenobillon (N.A.B.), novostab, rhodarsan. The second derivative is the *N* : *N'*-dimethylenebisulphite (formula IVb) which is sulpharsphenamine (B.P.) and for which kharsulphan, metarsenobillon, myosalvarsan, sulfarsenol and sulphostab are brand names.



(IVa): R=H; R'=·CH_2·O·SON. (IVb): R and R'=·CH_2·O·SO_2Na.

Symmetrical ureas (*Carbamides*).—The first and best known of this group of trypanocidal drugs is Bayer 205 or germanin. Its constitution was not disclosed by the proprietors, and in 1924 FOURNEAU and collaborators (1924, **21,** 379) described the production of a symmetrical urea of *m*-aminobenzoyl-*m*-amino-*p*-methylbenzoyl-1-naphthylamino-4 : 6 : 8-trisulphonate of sodium (formula V), which is now manufactured in France under the name Fourneau 309 (moranyl). As to the relationship of this substance to germanin, BAUER and BECKER have stated (1930, **27,** 67) that there can hardly be any doubt that Fourneau has found the right formula. According to a preliminary announcement (*Chemistry and Industry*, 1934, **53,** 836) the systematic name given above also applies to antrypol. Naganol is a form of germanin for veterinary use.



(V)

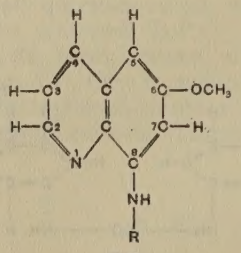
Alkaloids.—Though a number of drugs used by natives in the Tropics as anti-malarials have been examined in recent years and found to yield characteristic and well-defined alkaloids, none of these has proved of sufficient activity to come into use, and the cinchona alkaloids remain the sole anti-malarials of this group. Even these familiar substances have added to the nomenclature of drugs as the result of efforts to present them in more advantageous forms.

Tebetren is said to be " compounded of derivatives of quinine, acridine, etc., for the treatment and prophylaxis of malaria," whilst another

statement describes it as " prepared by a special process, combining acridine and quinine derivatives with a derivative of cholic acid " (*cf.* 1933, **30,** 84 ; 1934, **31,** 693). Malarcan seems to be a similar product (1935, **32,** 113).

The mixture of crystalline cinchona alkaloids known as quinetum has been given a definite modern standard by the Malaria Commission of the League of Nations, who have also rendered cinchona febrifuge unnecessary by the introduction of the improved and standardized mixture known as totaquina (1932, **29,** 461). Variants and precursors of totaquina in which the bases are converted into sulphates producing a more soluble product are panchina (1929, **26,** 23) and the chineto No. 1 issued by the Italian State Factory (1932, **29,** 712). Where cinchona febrifuge is still used, it is perhaps worth while to remind medical men of the useful standard suggested for this drug by FLETCHER (Notes on the Treatment of Malaria with Alkaloids of Cinchona, London, 1923, p. 3), though it is to be hoped that the recommendation of the Malaria Commission of the League of Nations (*loc. cit.*) that cinchona febrifuge should be replaced by totaquina will be generally acted upon.

Quinoline Derivatives.—The introduction of beprochin, since renamed plasmoquine, gave an enormous stimulus to the search for new anti-malarials. Although the starting point of the investigation which eventually led to plasmoquine is stated to have been methylene blue, plasmoquine has a closer relationship to quinine than to methylene blue. Its constitution was announced officially in 1928 (*Arch. f. Schiffs- u. Trop.-Hyg.*, 1928, **32,** 382) as 6-methoxy-8-diethylamino-*iso*pentylaminoquinoline, and a considerable number of similarly-constituted drugs have been synthesized in recent years in this country, France and Russia. Those that have been tried clinically are for the most part 6-methoxyquinolines with a dialkylaminoalkylamino- side chain in position 8 (see formula VI) and, as the following table shows, it is the length and nature of this chain which is the principal source of variation.



(VI)

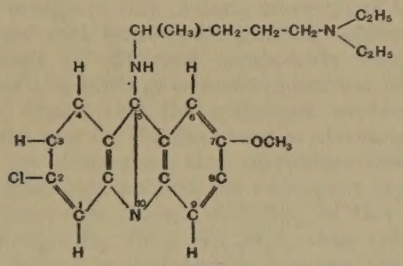
In plasmoquine R= —$CH(CH_3).CH_2.CH_2.CH_2.N(C_2H_5)_2$.
In related substances its character is as shown in the table below.

Name of Drug.	*Character of side-chain.*
Plasmoquine	$.NH.CH(CH_3).CH_2.CH_2.CH_2.N(C_2H_5)_2$.
Fourneau 710 (Rhodoquine)	$.NH.CH_2.CH_2.CH_2.N(C_2H_5)_2$. (1932, **29,** 348).
Fourneau 574	$.NH.CH_2.CH_2.CH_2.N(CH_3)_2$. (1933, **30,** 849, 850).
Fourneau 664	$.NH.CH_2.C(CH_3)_2.CH_2.N(C_2H_5)_2$. (*Ann. Inst. Pasteur*, 1931, **46,** 537).
Fourneau 852	$.NH.(CH_2)_{11}.N(C_2H_5)_2$. (1934, **31,** 175).

The Russian product plasmocide is described by the same chemical name as Fourneau 710 (1934, **31,** 174, 698). Fourneau 852 is also issued with sodium stovarsol as Fourneau 915 or Rhodoquine U (1933, **30,** 850 : 1934, **31,** 432, 433).

Acridine Derivatives.—A considerable number of reviews in this *Bulletin* deal with peracrina 303 as an anti-malarial drug. This product is stated to be a preparation of 2 : 8-diamino-10-methylacridinium chloride, which is acriflavine (B.P.), also known as trypaflavine and gonacrine. Acridine derivatives are also stated to be present in tebetren and malarcan in admixture with a cinchona alkaloid (*see above*).

The success which attended the insertion of a dialkylaminoalkylamino- side-chain in 6-methoxyquinoline, naturally led to the examination of the results of such insertions in other heterocyclic nuclei, and from this arose atebrin, which is 2-chloro-5-diethylamino-*iso*pentylamino-7-methoxyacridine (MAUSS and MIETZSCH, *Klin. Woch.*, 1933, **12,** 1276). Atebrin, therefore, contains the same side-chain as plasmoquine with the 6-methoxyquinoline nucleus of the latter replaced by a 2-chloro-7-methoxyacridine nucleus (formula VII). The constitutional name assigned to quinacrine (1934, **31,** 698) is identical with that of atebrin.



(VII)

Names of Substances mentioned.

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MALARIA.

GREEN (Richard). **Lectures on the Development and Use of the Synthetic Anti-Malarial Drugs.**—*Bull. Inst. Med. Res. Federated Malay States.* 1934. No. 2. pp. iv+50. With 7 figs. [39 refs.]

A useful paper on the history and efficiency of these drugs. Fewer recrudescences occur after atebrin than after quinine.

About 80 years ago, a search was begun for a synthetic substitute for quinine, and, in 1856, while PERKIN was engaged in this work he accidentally discovered the first of the coal-tar dyes. Eleven or twelve years ago, research on the problem of evolving a synthetic drug for malaria was, in general, mainly a matter of : (1) Trying to build up the molecule of quinine by synthetic means. (2) Modifying the structure of EHRLICH's anti-syphilitic arsenicals, so that they would destroy not only the benign tertian parasite, but the subtertian and quartan parasites as well. (3) Modifying the structure of methylene blue so that its action on the quartan parasite would be stronger, and so that it would also be effective against the benign tertian and subtertian parasites. Attempts to build up the molecule of quinine continued to fail. Stovarsol was evolved as a " spirocidal " drug, but was found also to be effective in benign tertian malaria when given by the mouth ; it had to be combined with quinine for treating subtertian and quartan malaria. Thousands of different compounds were evolved. Fortunately the malaria of birds gave some indication of the antimalarial efficacy of these drugs, and the technique evolved by ROEHL at Elberfeld paved the way for the discovery of plasmoquine and atebrin.

Starting with the observation that methylene blue has some antimalarial action, SCHULEMANN and his colleagues replaced one of the short dimethylamino- side chains, $-N(CH_3)_2$, of this dye-stuff by the longer chain $-N(CH_3).CH_2 .CH_2 .N(C_2H_5)_2$, thus enhancing the antimalarial action. It was an obvious step to repeat the experiment with the quinoline, instead of the methylene blue, nucleus and after that to try the effect of changes in the position, length and character of this substituent, the part of the research which led to plasmoquine (see figure VI, HENRY and GRAY'S article, p. 388), and, this point being settled, to try the selected substituent in other heterocyclic nuclei including acridine, which led eventually to atebrin (see figure VII, p. 389).

It soon became established that plasmoquine had little or no action on the rings and schizonts of subtertian, and next a reversion was made to a triple ring system instead of the double ring system of the quinoline nucleus. The triple ring system, however, which was finally used was that of acridine instead of methylene blue, and atebrin was the result. It is said that the widening of the ring system in atebrin was aimed at with the object of getting rid of the toxic properties associated with the quinoline nucleus.

The ring system is similar in quinine and plasmoquine—each drug has a quinoline nucleus—although it will be noted that the ring system (or quinoline nucleus) of plasmoquine has undergone, as it were, a complete turn through half a circle prior to being linked up. In atebrin the ring system is different, atebrin has an acridine nucleus. The basic side-chains of plasmoquine and atebrin are identical, that of quinine is distinct and highly complex.

FOURNEAU and his colleagues have produced a large series of compounds of which about 40 have some effect upon the malaria of birds. Certain of these compounds were selected for tests on man; for example Fourneau 710, 574, 852 and 915 (see HENRY and GRAY's article, pp. 330, 388, 389). Both 710 and 574 act like plasmoquine; they have all its defects and are somewhat less effective as regards their action on the benign tertian and quartan parasites. Fourneau 852 is said to be less toxic and to be active against all forms of malarial parasites. Fourneau 710 is easier to prepare than plasmoquine.

Russian chemists have produced a compound which they call "Plasmocide" or "Antimalarene B." It acts like plasmoquine. English workers have recently evolved a number of new quinoline compounds. As judged from tests on birds the results with two of them are regarded as encouraging, but they seem likely to produce methaemoglobinaemia, as plasmoquine does.

The quinine derivative (C.77) prepared experimentally by Professor GIEMSA is a red azo-dye, made by coupling hydrocupreine (hydroquinine is the methyl ether of hydrocupreine, just as quinine is the methyl ether of cupreine) with diazotised 6-methoxy-8-amino-quinoline and may be represented by the simple linear formula :—

$$CH_3O.C_9H_5N— N : N—C_{19}H_{24}O_2N_2$$

6-methoxyquinoline-8-azo-hydrocupreine

The author has treated 21 cases with it. It appeared to act like quinine on the parasites of subtertian and quartan malaria, but to be definitely inferior in benign tertian. It was free from such side effects as deafness, tinnitus, etc. The dose given was about 9 grains daily for 7 days.

Totaquina, tebetren and esanofele, are dealt with under the section of "Drugs containing quinine." "Clinically totaquina is slightly less efficacious than quinine but could replace it in many circumstances." Tebetren is said to consist of a mixture of hydroquinine, acriflavine and bile salts. The author writes "Tebetren is . . . five times more costly than quinine and is no better than quinine in its effect on relapses. . . . I have been unable to find any reasons on the grounds of increased efficiency or lessened toxicity for substituting such an expensive drug for quinine or atebrin." Esanofele is widely advertised as a specific for malaria. The composition of each pill is said to be as follows: Quinine bisulphate gr. 1/3, Arsenious acid gr. 1/100, Citrate of iron gr. 2/5. The danger lies in esanofele being accepted as a remedy for acute attacks, while it is really a pill for use in convalescence.

As regards the use of plasmoquine as a means of reducing the transmission of malaria, the author writes :—"It will be noted that the only known successes have been achieved when the *whole* population has been under *regular and continuous* plasmoquine treatment, also that any good results have been lost within a short time after such regular treatment of the whole population has ceased . . . it would seem that anti-gametocyte measures should remain subordinate to anti-larval measures until it can be shown that, in the particular circumstances, better results can be achieved more conveniently, with similar certainty, and at less cost by the use of synthetic drugs. How to *combine* the two measures successfully would appear to be a matter entirely for local judgment in each case."

"Atebrin," he writes, "is the first available drug which can be used in giving effective 'mass' treatments to a large working population, because

it can be given in 'curative' doses at one daily muster and does not interfere with working efficiency as quinine does when given in 'curative' doses. . . . A small but certain proportion of patients under treatment with atebrin have shown: (*a*) *Unpleasant by-effects* consisting of (1) mild headache; (2) Mild abdominal pains; (3) Yellowish discoloration of the skin or whites of the eyes. Such symptoms or signs have occurred in about 2 per cent. of patients under my care. Some of these patients, however, were given larger doses, or longer courses, of the drug than usual. . . . (*b*) *Toxic symptoms.* Under this heading are included: (1) Severe and persistent headache; (2) Severe abdominal pains; (3) So-called 'cerebral excitation.' Such symptoms have occurred in about 1 per cent. of my patients some of whom, again, were given larger doses or longer courses of the drug than usual . . . The term 'cerebral excitation' requires some further explanation. Briefly, it consists of an excited mental state lasting sometimes about 24 hours or longer. Such a condition occurred in two of my patients, both of whom were treated for severe sub-tertian malaria with atebrin for a period of 7 days. One case will be described. . . . Treatment with atebrin, 3 tablets daily, was continued for 7 days . . . he entered upon a curious phase . . . 6 days after the course had ended . . . sang and danced in the ward, appeared to find the greatest amusement in everything going on round him, laughed frequently without apparent cause, and appeared to be in a generally hilarious state. He remained like this for about 24 hours and 'settled down' during the following day . . . said he felt as if he had been drunk."

Dr. Green considers that before forming any opinion on the use of *Atebrin as a Clinical Prophylactic*, it would be necessary to have the results of prolonged and well conducted experiments. He does not think that it would be safe to give sub-curative doses of atebrin, say 0·1 gram daily, over long periods, because of possible cumulative effects. In connexion with the *Prevention of Relapses by Atebrin*, he treated 63 cases with 3 tablets of atebrin daily for seven days and observed them for a subsequent period of 27 days; 3 cases or 4 per cent. relapsed. A control series of 53 cases was treated with 30 grains of quinine daily for 7 days. They were then observed for an average period of 18 days only, and 20 cases or 38 per cent. relapsed. The vast majority of patients in the tropics are available for treatment for short periods only (usually not more than 7 days). *W. Fletcher.*

Union of South Africa. Annual Report of the Department of Public Health Year ended 30th June, 1934. [**Malaria** pp. 45–58.]

The principal anti-malaria measure adopted is the killing of adult mosquitoes in dwellings by means of a spray.

The 1933–4 season was exceptionally wet, warm weather persisted a month over time into May, breeding of *A. gambiae* occurred on a large scale, cases of fever appeared over a wide area and there were some cases of blackwater fever. The proportion of deaths was much lower than in the past, and this is attributed to the fact that the whole population is gaining knowledge of malaria control and is turning its attention to preventive measures on an organized basis in addition to fighting the disease by immediate treatment as soon as it occurs. Killing adult mosquitoes in dwellings by spraying is the chief method of control. Mosquitoes are easily destroyed in the typical Zulu beehive hut which is usually smoke-laden. The insecticide used is " Pyagra," which is diluted 1 in 17 with paraffin and applied by means of a spray pump. General larval control is impracticable in most native reserves,

but there is hope of solving the malaria problem by supervised spraying, with or without limited larval control. Malaria is endemic in some of the reserves, and the natives have acquired a certain degree of immunity which makes them of special value for work on sugar estates where conditions are unsuitable for non-immune labour. Following the advice of Professor SWELLENGREBEL, no anti-malaria work is being attempted in those reserves with an immune population. Elsewhere, a great deal of propaganda has been carried on; at first the people were suspicious, or even hostile, until the effects of treatment were noted. "It has been shown that anti-malaria control is perfectly feasible in a native area, always provided that it has had a sharp epidemic as a preliminary and that methods of control are introduced tactfully." The mass of the population takes tablet quinine. There has been opposition instigated by native herbalists, but now most of them sell quinine themselves under some disguise or other. One of them pointed out to his customers that whereas the Government supplies were undoubtedly suited to white people, because they had white skins, his medicine had a black spot without which the tablets were useless for natives. He had bored a hole in each tablet and filled it with a mixture of soot and fat. *W. F.*

ANNECKE (S.). **Malaria Control in the Transvaal.**—*South African Med. Jl.* 1935. Jan. 12. Vol. 9. No. 1. pp. 3–7.

This deals with gambiae-malaria and funestus-malaria. The people need food rather than advice.

Control of malaria along modern lines has been established only recently in this province, more especially since the receipt of a report to the government by Dr. SWELLENGREBEL. There are two main vectors, (1) *A. gambiae*, the puddle-breeder, breeds in shallow depressions in the ground which are clear of vegetation and exposed to sunlight. It spreads with rainfall. The malaria of the Bushveld is gambiae-malaria. (2) *A. funestus* breeds at the edges of streams or rivers, where shade is plentiful and the current is slow. The malaria of the Lowveldt is funestus-malaria. In gambiae areas antilarval work is put first, because the puddles can be dealt with by draining, filling, or oiling with waste engine-oil to which a little paraffin has been added. In funestus areas, antilarval work is hopelessly impossible from a financial point of view. In these places anti-adult measures such as screening and insecticides must be adopted. "The difficult times through which farmers have passed have left in their wake a mass of people who, though not actually starving, are in very straitened financial circumstances. . . . We teach prevention, and in many homes there is not the wherewithal to buy the daily mealie meal, let alone think about prevention of malaria. Proper feeding . . . is most important in fighting the continual ravages of recurring malaria." The author has a staff of health visitors who visit the homes and give instruction in diet, domestic hygiene and child-welfare. He has drawn up a standard antimalarial treatment which is being adopted by district surgeons, and by practitioners in malarious areas. The control unit of the Department of Public Health does not act executively; it spends no money in the control of malaria, but visits the farms, gives advice and makes inquiries. *W. F.*

Anning (C. C. P.). **Meteorological Factors in the Incidence of Malaria in Pietermaritzburg.**—*South African Med. Jl.* 1934. Dec. 8. Vol. 8. No. 23. pp. 875–878. With 3 charts.

Malaria has spread to Pietermaritzburg which was free from it until about 6 years ago.

The author discusses the possible causes of the spread of malaria from the coast to Pietermaritzburg. The town lies about 50 miles inland at an elevation of 2,100 ft. above sea-level, in a valley surrounded by hills. Several cases of malaria are said to have occurred in 1906, but the evidence is unreliable. No further case infected within the borough was reported until 1929, when a few cases occurred in the eastern side of the town nearest to the coast. There is no record of the number of infections in 1930 and 1931, because notification was not in force, but, between January and May 1932, at least 1,500 new infections occurred. The deaths due to malaria among borough residents were :— 1929, nil ; 1930, 3 ; 1931, 20 ; 1932, 105 ; 1933, 25. Extensive drainage and anti-larval and anti-mosquito measures were undertaken in 1933 ; " to these, to a large extent, is ascribed the marked reduction in the number of infections during the 1933 season." The vector is *A. costalis*, and the principal breeding places have been in muddy water exposed to the sun. It is difficult to understand why malaria has spread to the healthy town from the coast where it is endemic. The author writes :—

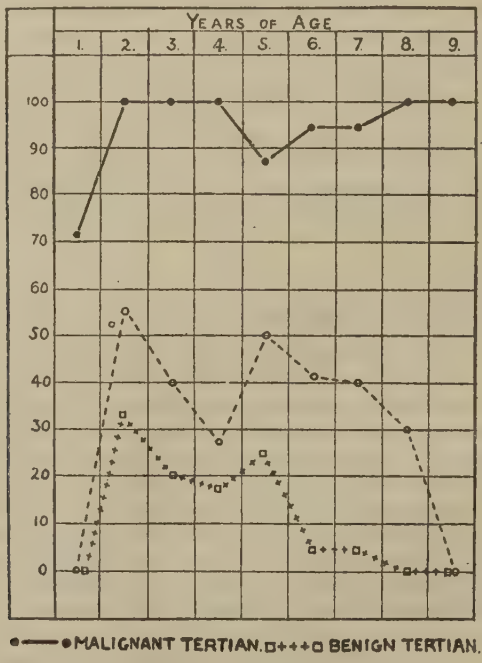
" How far the gradual reduction in total rainfall, associated with an increase during March (the centre of the breeding season), together with a fall in the mean daily temperature during the breeding months of January–April, and a fall in the relative humidity figures for the same period, has made more easy the settlement of *A. costalis* in Pietermaritzburg, I cannot assess . . . The incrimination of road and rail transport as regards the importation of *A. costalis* into Maritzburg rests upon unproven accusations." *W. F.*

Thomson (J. Gordon). **Malaria in Nyasaland.**—*Proc. Roy. Soc. Med.* 1935. Feb. Vol. 28. No. 4. pp. 391–403 (Sect. Trop. Dis. & Parasit. pp. 11–23). With 4 charts. [35 refs.]

A. gambiae is a more important vector than *A. funestus*. Inherited immunity and tolerance exist among natives. Little illness is caused by infection in older children and adults, but many infants die. Prophylactic quinine should be taken by Europeans.

The chief vectors of malaria in Nyasaland are *A. gambiae* and *A. funestus*. The months of June, July and August are practically rainless ; *A. gambiae* disappears and though *A. funestus* is plentiful there is very little malaria. The rains begin in October, swarms of *A. gambiae* appear, malaria increases rapidly and, later on, cases of blackwater fever occur. There have been 157 cases of blackwater in 23 years, with a case mortality of 30 per cent. The cases occur outside the areas controlled by European communities, principally among people who neglect to take precautions and " neither protect themselves from the onslaught of mosquitoes, nor take quinine as it should be taken." An examination of 103 children made once a month for a whole year showed that some were much more susceptible than others. Four of the children remained consistently negative. This varied resistance in children under 10 years seems to indicate that certain individuals have an inherited tolerance ; it has been estimated that only 10 per

cent. live to the age of 6 years*, and possibly it is to a large extent those with inherited tolerance who reach adult age. *P. falciparum* was present in 96 of the 99 infected children, *P. malariae* in 35, and *P. vivax* in 9. During the height of the malaria season, native children up to the age of 2 years frequently have as many as 3 or 4 parasites to one red cell, and many of them die from convulsions. Tolerance is soon developed, and, except in very young children, malaria causes little illness. The children seen in this survey showed few manifestations of malaria and all those who were old enough to walk could run about as if they were perfectly healthy, although they had parasites in their blood. No cases of congenital infection were seen, and the author concludes that "malaria contracted *in utero* is a rarity. . . . The phagocytic picture exhibited by . . . placental smears affords a remarkable demonstration of the active part played by the large mononuclear macrophages and the polymorphonuclear leucocytes as controlling factors, modifying the course of the infection." *P. vivax* infections decrease as age increases, and show the most rapid fall; this is followed by a drop in quartan, but *P. falciparum* persists till at least 9 years of age, without showing any fall in the numbers infected, see Chart. Gametocytes are most numerous in children who are 2 or 3 years old,



Percentage of children infected, according to age. (Based on monthly examinations of a group of 103 native children in Nyasaland throughout the year.)

[Reproduced from the *Proceedings of the Royal Society of Medicine.*]

* This ninefold decimation of young children is almost Herodian. The Annual Report (1932) gives the estimated death-rate as about 400 per 1,000 live births, up to the age of 6 years, which is surely high enough. [See this *Bulletin*, 1933, Supp., p. 57*.]

and they decrease as the children become older. The gradual development of resistance to infection is also shown by the fall in the spleen rate between the ages of 5 and 10 years.

A dose of 5 grains of quinine should be taken with absolute regularity by Europeans as a prophylactic wherever malaria is hyperendemic, the population scattered, and protection from malaria difficult. Monseigneur Guillenié published his experiences of blackwater fever in the "Nyasaland Times" in 1934. The White Fathers began to establish Central African Missions in 1878, and during the succeeding 28 years, 200 of them died from blackwater. During the last 28 years they have taken prophylactic quinine, and none of them has died from blackwater. *W. F.*

Foley (H.) & Parrot (L.). L'assainissement de l'oasis d'El Goléa. La question du paludisme. [**The Sanitation of the Oasis of El Golea.**]—*Arch. Inst. Pasteur d'Algérie.* 1934. Dec. Vol. 12. No. 4. pp. 471–484. With 6 figs. on 3 plates & 1 plan.

The sinking of numerous artesian wells has led to the formation of lakes and swamps, which give rise to malaria.

The oasis of El Golea is one of the most beautiful in the Algerian Sahara. It was healthy when it was first occupied by the French in 1891, but malaria followed the introduction of irrigation, and in the year following the sinking of artesian wells there were 68 cases; in 1907 there were 500 cases; in 1927 there was an epidemic of subtertian. A survey made by the authors showed that the disease was not very intense at the present time, but that there were numerous marshes and lakes in which the larvae of *A. multicolor* and *A. sergenti* were breeding. They consider that oiling, the introduction of larvivorous fish and the like, would be of little use. What is needed is the supervision and regulation of irrigation, and the provision of efficient drainage to carry off the water. *W. F.*

Egyptian Government. **Anti-Malaria Commission. Report No. 9 of the Anti-Malaria Commission for the Fiscal Year 1932–1933.**—8 pp. With 4 folding plans. 1934. Cairo: Govt. Press, Bulâq. [P.T.5.]

Gives the number of cases of malaria reported in Cairo and other towns.

The Ministry of Finance granted L.E.10,000 for anti-malaria work during 1932–33. The amount spent was L.E.8,116, and this report shows how the sum was distributed among the different towns and villages. In a village near Cairo where three swamps were filled, the contractor obtained the necessary earth from borrow-pits. "The Main-drainage Department placed the amount due to him in suspense account pending the filling in of these borrow-pits." Nearly 200,000 larvivorous fish (Bolti, Cyprinodon, Gambusia) were distributed in swamps and water channels. The number of cases of malaria reported to the Public Health Administration, during the year 1932, was 1,343 with 23 deaths. Sixty-two cases with no deaths, were reported from Cairo; 232 cases, 2 deaths, from Alexandria; 36 cases, 7 deaths from Ismailia; 15 cases, no deaths, from Port Said; 89 cases, 2 deaths, from Suez. *W. F.*

Khalil Bey (M.). **Combatting Mosquitoes and Malaria in Alexandria and its Environments. (A Report to H.E. the Undersecretary of State for Public Health.)**—*Jl. Egyptian Med. Assoc.* 1934. Dec. Vol. 17. No. 12. pp. 943–958.

The incidence of malaria in Alexandria during the last four years was as follows :—1931, 98 cases ; 1932, 282 ; 1933, 303 ; first half of 1934, 143. " Antimalaria projects are not welcomed by administrators . . . administrators prefer the erection of edifices such as a club, a hospital, a museum or a road like the Corniche or a public garden, because such projects are always before the public eye. . . . Malaria can be controlled with success in Alexandria if the necessary means are available."

W. F.

Knowles (R.) & Basu (B. C.). **Mosquito Prevalence and Mosquito-borne Diseases in Calcutta City.**—*Records of the Malaria Survey of India.* 1934. Sept. Vol. 4. No. 3. pp. 291–319. With 11 charts & 1 fig. [38 refs.]

Malaria in Calcutta is attributed to the poor water supply.

The authors give in this paper the results of observations carried out in an area, one square mile in extent, around the School of Tropical Medicine in the centre of Calcutta. " Malaria is not apparently a very serious danger to Calcutta City, but we have already one virulent mosquito carrier—*Anopheles stephensi*—breeding in almost every other water storage receptacle in the city, together with the recent introduction of a second, and even more virulent carrier, *Anopheles sundaicus* (*A. ludlowi*). The future is quite uncertain." *A. stephensi* breeds, for the most part, in vessels which are used for storing water ; *Aëdes aegypti*, the carrier of dengue, and *Culex fatigans*, the carrier of filariasis, breed in the same places as *A. stephensi*. The low pressure and intermittent character of the water supply are responsible for the prevalence of mosquito-borne diseases in Calcutta. The remedy is the provision of a continuous water supply at high pressure. A figure given in the text shows 21 different kinds of receptacles in which *A. stephensi* was found.

W. F.

Basu (B. C.). **A Brief Survey of Malaria and Anopheline Fauna in Patna.**—Reprinted from *Patna Jl. of Med.* 1933. July. Vol. 8. No. 3. pp. 152–160. With 5 figs.

An increase of malaria due to interference with drainage.

Patna is the capital of Bihar and Orissa. It extends for 15 miles along a narrow strip of land, about a mile wide, compressed between the Ganges on the north and the East Indian Railway line on the south. The malaria curve almost coincides with that of the rainfall ; it rises in the spring, reaches its maximum in August, and then falls. The principal carriers of malaria are (1) *A. culicifacies*, which breeds in the railway ditches and in the borrow-pits of brickfields, and (2) *A. fuliginosus* which breeds in the lakes, ponds and ditches. The prevailing type of malaria is subtertian. *A. stephensi* was not found, although there are innumerable wells and water receptacles because only a part of the town is provided with a water supply and even that is intermittent. The town slopes away from the river, and the drainage runs into a swamp on the south of the railway ; when the Ganges is in flood,

a large part of the town lies below its level. In former days, the swamp drained into the river; the author implies that, since this drainage has been blocked, there has been an increase of malaria and a decrease in the population. *W. F.*

Covell (G.) & Baily (J. D.). **Malaria in Sind. Part XII. A Note on Malaria in a Water-Logged Area in Khairpur State.**—*Records of the Malaria Survey of India.* 1934. Sept. Vol. 4. No. 3. pp. 327–341.

Increase of malaria attributed to waterlogging due to irrigation by the Lloyd Barrage.

The south-eastern portion of the State is part of a great desert supporting a scrubby vegetation which affords grazing to camels. The north-western part is very fertile where it is irrigated. The average rainfall for the last 13 years is less than 4 inches. The climate is cold in winter, when severe frosts are not unknown, but in summer it is very hot and the thermometer may rise to 120°F. As the result of seepage from the great new Rohri Canal, a considerable area in Khairpur State became completely waterlogged almost immediately after the opening of the Lloyd Barrage in 1932. A survey made in December 1933 showed that the spleen-rate in 14 water-logged villages was 86 per cent. In 11 which were not water-logged it was 63 per cent. A remarkable feature of the survey was the great preponderance of *A. stephensi* over the other species of anophelines captured. The authors consider that the great rise in the subsoil water, following the Barrage, has been the direct cause of the increase of malaria. *W. F.*

Nursing (D.), Rao (B. A.) & Sweet (W. C.). **Notes on Malaria in Mysore State. Part VII. The Anopheline Transmitters of Malaria.**—*Records of the Malaria Survey of India.* 1934. Sept. Vol. 4. No. 3. pp. 243–251.

Anopheles were caught in an endemic area in houses and cattle sheds, and in a tent with a human bait. They were caught in one district during an epidemic. The authors conclude that *A. culicifacies* and *A. fluviatilis* are the important carriers in the rural areas of Mysore. The former appears to use habitations as a daytime resting place, the latter prefers other situations. In the endemic area, the oöcyst rate of *A. culicifacies* was 2·5 and the sporozoite rate 0·2 per cent., the corresponding rates for *A. fluviatilis* were 2·4 and 0·8 per cent. In the epidemic area, infections were found in *A. culicifacies* only; the rates being 2·3 per cent. for oöcysts, and 1·0 per cent. for sporozoites.

W. F.

Clemesha (W. W.). **Brief Account of the Natural History of Malaria in Ceylon.**—*Ceylon Jl. Sci.* (Sect. D. Med. Sci.). 1934. Dec. 8. Vol. 3. Pt. 3. pp. 157–172. With 2 graphs (1 folding).

Malaria in Ceylon occurs at the end of the dry season. When there is plenty of rain there is little malaria.

There is only one carrier in Ceylon, *A. culicifacies*. Other anopheles occur which are important vectors in other countries, for example *A. maculatus* and *A. funestus*, but here they do not bite man. *A. culicifacies* breeds in shallow pools and puddles in the beds of streams when

they are almost empty during dry weather, particularly in flat country at the foot of the hills. It is useless to look for the larvae except in sunny places, and the water must be clear. The normal increase of this species takes place in the hot weather immediately preceding the rains. In the northern part of the island, the dry weather and the period of increase of *A. culicifacies* occur in July, August and September. In the south-east, the period of drought and anopheline breeding is February, March and April. In the south-west part of the island droughts are very rare, and so is malaria. [It is in this district that the great epidemic has occurred following a drought.] *A. culicifacies* is a domestic mosquito; when its normal breeding places are not available it will seek others. Where there are no streams, or where these are polluted, it will breed in wells. It does not breed in paddy-fields, and these are not a cause of malaria in Ceylon. The healthy years in Ceylon are always those in which the July, August and September rainfall is plentiful, that is to say above 20 inches. Unhealthy years are those in which it is scarce, or under 20 inches. *W. F.*

DÀNG-HANH-KIÊN. Le paludisme à Phong-Thó. [**Malaria at Phong-Tho.**]—*Bull. Acad. Méd.* 1935. Feb. 5. 99th Year. 3rd Ser. Vol. 113. No. 5. pp. 183–191.

This describes the premunition of the indigenous tribes.

Phong-Tho is one of the most unhealthy districts of Upper Tonking, and can be reached only after a long and dangerous journey through virgin jungle and along precipitous mountain sides. Though the total population numbers only about 12,000, it comprises several races which differ in their languages and customs. Everyone becomes infected with malaria, but the indigenous natives suffer comparatively little inconvenience from it, and the adult splenic index is only 19 per cent. The immigrant Europeans and Annamites, on the contrary, suffer severely; blackwater fever is not uncommon among them and occurs independently of quinine. The adult splenic index is nearly 4 times higher than that of the indigenous races. The author carries out his work in the face of great difficulties. He sees his patients in a shed which leaks in the rainy weather; if he decides to treat any of them as in-patients he must provide for their maintenance at his own cost; he has no microscope; he suffers from malaria. One feels on reading this paper that it is a message from a brave colleague. *W. F.*

ROBIN (L. A.). Évolution de l'état sanitaire des collectivités ouvrières agricoles importées en région d'hyperendémie palustre. Influence de la "prémunition acquise." [**The Influence of Premunition on the Development of Healthy Conditions among Labourers in Hyperendemic Areas.**]—*Rev. d'Hyg. et de Méd. Preventive.* 1935. Jan. Vol. 57. No. 1. pp. 30–42.

Antilarval measures are essential in the prevention of malaria on rubber estates.

The opening up of rubber estates in the malarious jungle of southern Indo-China and the importation of labour from non-malarious districts were followed by disastrous outbreaks. When prophylactic quinine and antilarval measures were applied in combination, amelioration soon followed, but where reliance was placed upon quinine alone conditions often became worse; on some estates, one-fifth of the coolies died in

the course of a few months, and the estates were perforce abandoned. On many estates, however, though no antilarval work was done things gradually improved, the daily turn-out of labourers was better, there were fewer sick and fewer deaths, and, after about 5 years, some places appeared to have become healthy without any expenditure on antilarval measures. The introduction of fresh, unsalted labourers into such an estate is always followed by an outbreak of malaria ; which shows that the place is still malarious and that the reason why the old labour does not suffer is because it has become tolerant or immune. The children on such an estate, who too may be considered as newcomers, also suffer severely. Labour will never remain contented on an estate where nearly all their children die, and this will make things very difficult when contract labour is abolished, and it becomes necessary to import "free" labour.

The history of malaria on the plantations of Cochin-China and Cambodia has shown that antilarval measures must take the first place in prevention. *W. F.*

Monier (H. M.), Guy (R.) & Ros (M.). Renseignements sur le paludisme recueillis dans les régions de Luang-Prabang et Paklay, au Laos. [**Malaria at Luang-Prabang and Paklay in Laos.**]—*Ann. de Méd. et de Pharm. Colon.* 1934. July–Aug.–Sept. Vol. 32. No. 3. pp. 309–327.

Luang-Prabang, the capital of the Kingdom of the Million Elephants and the White Parasol, is a pretty little town situated in the valley of the Mekong River, 6,500 feet above sea level. It is surrounded by jungle and contains innumerable sacred lakes. About a quarter of the cases treated at the hospital are due to malaria. The spleen rate determined by the authors was 16 per cent. in the centre of the town, but it was much higher on the outskirts, where it reached 78 per cent. in some districts. The parasitic index was 38 in this malarious area ; in the centre of the town it was only 5·76.

Paklay is situated on the Mekong below Luang-Prabang, and contains a large native population because it is an important place on the caravan route between Laos, Siam and Burma. The town is traversed by innumerable small streams which run into the Mekong. They serve as breeding places in the wet weather ; in the dry weather they dry up, but breeding continues in pools on the sandbanks uncovered by the shrinking river. The splenic index in children under 15 is about 50 per cent., and the parasitic index about 15. *P. vivax* constituted 76 per cent. of the infections. This is the reverse of what is found in the hospitals where 96 per cent. of the malaria cases are due to *P. falciparum.* The reason for this is that many of the people infected with *P. vivax* have no symptoms and therefore they do not go into hospital, *P. malariae* was found almost exclusively in children between 3 and 15 years of age, and *P. falciparum* in children over 15. *W. F.*

Russell (Paul F.). **Malaria and its Control in the Philippines.**—Reprinted from *Sugar News.* 1934. Nov. Vol. 15. No. 11. 6 pp.

An important paper. The local cultivation of cinchona and the manufacture of totaquina is advocated. This is a popular exposition of the causes and prevention of malaria in the Philippines which

contains many interesting facts and expressions of the author's opinions.

Malaria is serious and widespread in the Philippines; one may safely estimate that it kills from 10,000 to 20,000 Filipinos annually; there are probably two million cases a year throughout the islands, but in the cities of Manila, Cebu and Iloilo there is little or no malaria. There are only two carriers, and both of them breed in running water; they are:—*A. minimus* var. *flavirostris* and *A. maculatus*. The small streams at the foot-hills are the home of these mosquitoes; the lowlands, and the highlands above 2,000 feet, are not malarious.

Relatively few of the Filipinos can afford suitable treatment with quinine, but recent co-operative studies by the Bureaux of Science, Forestry and Prisons, together with the Rockefeller Foundation, have shown that an excellent totaquina could be made in the Philippines to sell at about one-seventh of the price of quinine and yet to yield good profits to the grower, the manufacturer and the retailer. "There is a potential market in the Philippines alone for some 33 tons of this totaquina annually, without competing at all with the quinine and synthetic products now imported . . . totaquina is less bitter than quinine, has no bad effects and is equally efficacious. Totaquina would meet the need for an effective but much cheaper remedy. Furthermore, there would be a market for this totaquina in South China and it is possible . . . in the United States." *W. F.*

Russell (Paul F.). **Malaria and Anopheles Reconnaissance in the Philippines, II.**—*Philippine Jl. Sci.* 1934. May. Vol. 54. No. 1. pp. 43–59. With 2 figs. on 1 plate.

Extended observations have confirmed the author's conclusions published in an earlier paper (this *Bulletin*, Vol. 30, p. 462). A list is given of 27 species of anophelines found in the Philippines. *A. minimus* var. *flavirostris* and *A. barbirostris* are the most common. *A. barbirostris* has never been found infected, but *A. minimus* is the most important carrier in the country. The *funestus-minimus* subgroup has been greatly confused in the past; it seems likely that *A. minimus* var. *flavirostris* has included *A. funestus*, *A. minimus*, *A. filipinae* and *A. mangyanus*. *A. littoralis* King ("salt-water *ludlowi*") and *A. ludlowi* Theobald ("fresh-water *ludlowi*") are not associated with malaria in the Philippines. It appears that certain larvae which were hitherto called *A. umbrosus* are really *A. baezai*, Gater. Malaria is widespread throughout the Philippine Archipelago; it is primarily a disease of the foothill regions, being found wherever there are streams containing larvae of *A. minimus*. The littoral when flat, the inland plains, and the mountains above 2,000 feet are not malarious. *W. F.*

Russell (Paul F.). **The Small Spleen in Malaria Surveys.**—*Amer. Jl. Trop. Med.* 1935. Jan. Vol. 15. No. 1. pp. 11–32. With 1 fig. [20 refs.]

A splenic index of over 5 per cent. denotes malaria.

Not more than 5 per cent. of children in non-malarious areas, have a "palpable-on-inspiration spleen." In the author's experience 45·5 per cent. of the children with such spleens have parasites in their blood; he finds that the more malarious a community, the more numerous are the p-o-i spleens. An incidence of over 5 per cent. suggests either:

(1) A community malarious at the time of examination, in which case the total spleen index will be in excess of 10 per cent. (2) A community where malaria has occurred, but where no transmission is taking place at present. In this case the index will be between 5 and 10. (3) A non-malarious community into which children have recently come from a malarious district. Tuberculosis does not enlarge the spleen sufficiently to vitiate the index. About 15 per cent. of scarlet fever cases have a residual palpable spleen which may last for several years.

W. F.

Treillard (M.). Une modalité de la zoophilie anophélienne en Indochine méridionale : *Neocellia fuliginosa* à la station d'altitude de Dalat (Annam). Points de vue biologique et antipaludique. [**Anopheline Zoophilism in Southern Indochina.**]—*Bull. Soc. Path. Exot.* 1934. Oct. 10. Vol. 27. No. 8. pp. 754–756. With 4 figs. on 2 plates.

The author has studied the habits of *Neocellia fuliginosa* at the hill-station of Dalat in Annam. The inhabitants stop up every cranny in the walls of their houses at night because of the cold, but the cattle sheds which surround these houses are not built so carefully, nor are they hermetically sealed at night. Large numbers of *N. fuliginosa* are found in the cattle sheds, but none are found in the houses. This mosquito is a carrier in Burma, the Dutch Indies and British Malaya ; the author has infected it experimentally in Annam, but here it appears to have been deviated from man and to feed on animals. He considers it important that the existing equilibrium should be maintained by keeping animals in the neighbourhood of human dwelling places. He has found *N. fuliginosa* in some new barracks, where there were no stables in the vicinity. *W. F.*

Gaschen (H.). Infection naturelle de *Anophèles hyrcanus* var. *sinensis* (Wied. 1928) et la transmission du paludisme au Tonkin. [**Natural Infection of** *Anopheles hyrcanus* **var.** *sinensis* **in Tonking.**]—*Bull. Soc. Méd.-Chirurg. Indochine.* 1934. June–July. Vol. 12. No. 6. pp. 554–557. With 1 fig. [12 refs.]

A. sinensis is an important carrier in some countries such as the Dutch East Indies, while in others—British India for example—it has never been found infective. The author reports the sporozoite infection of a specimen caught in Tonking. He suggests that there may be different races of *A. sinensis*, some of which carry malaria and others which do not. *W. F.*

Galliard (H.) & Sautet (J.). *Anopheles sacharovi* Favr. (*elutus* Edw.) et *A. maculipennis* var. *labranchiae* dans leurs rapports avec le paludisme en Corse. [*Anopheles sacharovi* **Favr.** (*elutus* **Edw.**), **and** *A. maculipennis* **var.** *labranchiae* **in Relation to the Malaria of Corsica.**]—*Bull. Soc. Path. Exot.* 1934. Nov. 14. Vol. 27. No. 9. pp. 855–857.

No answer has been found to the question why some places on the coast of Corsica are so malarious and why others are healthy.

A. elutus is present in large numbers all along the coast, and it is also found in certain spots some kilometres from the sea. *A. maculipennis*

labranchiae is present in equal numbers in these places, and is also found in the valleys which run up into the hills. *A. maculipennis* var. *messeae* and var. *melanoon* are also present in small numbers.

The authors attempted to discover if the prevalence of malaria in certain districts was dependent upon the presence of certain varieties of *A. maculipennis*. No such relation appeared to exist ; the anopheline fauna of places where malaria was severe was the same and as numerous as that of many other places which were healthy. The conditions as regards cattle were apparently identical in malarious and in healthy places. The answer to the question has not yet been found.

W. F.

Boyd (Mark F.) & Stratman-Thomas (Warren K.). **The Comparative Susceptibility of** *Anopheles quadrimaculatus* **Say, and** *Anopheles crucians* **Wied. (Inland Variety) to the Parasites of Human Malaria.**—*Amer. Jl. Hyg.* 1934. July. Vol. 20. No. 1. pp. 247–257.

A. quadrimaculatus is the more susceptible to infection ; *A. crucians* is relatively unimportant.

Both species are widely distributed in Florida, but while about 1 per cent. of *A. quadrimaculatus* has been found infected in nature, and in one instance nearly 4 per cent., the rate for *A. crucians* is only 0·2 per cent. The authors found that while *A. quadrimaculatus* fed greedily on man, *A. crucians* could only with difficulty be induced to do so. Both species were infected when they were fed on patients whose blood contained large numbers of benign tertian or subtertian gametocytes, but when these were scanty, only *A. quadrimaculatus* was infected. In quartan cases, nearly one-fourth of the *A. quadrimaculatus* became infected, but none of the *A. crucians*. *W. F.*

Pecori (G.) & Escalar (G.). Relazione sulla campagna antimalarica nell' Agro Romano durante l'anno 1933. [**The Antimalarial Campaign in the Agro Romano in 1933.**]—*Riv. di Malariologia.* Sez. I. 1934. Vol. 13. No. 5. pp. 623–668. With 2 graphs & 1 map. English summary.

Malaria was much less severe in 1933 than in previous years. The inhabitants of the controlled area numbered 74,595. The malaria morbidity was 1·98 per cent. Only one death from malaria and one from blackwater occurred during the year. The splenic index of 7,299 school children was 4·6 per cent. The parasite index was 0·87 per cent. " A part of the Roman Suburbs and the Agro had been annexed to the territory of Rome City, and with a Royal Decree (8th May 1933) the entire Suburbs of Rome and the ' Lido ' with Castel Fusano Park were declared free from malaria." *W. F.*

Boyd (Mark F.), Stratman-Thomas (Warren K.) & Muench (Hugo). **Studies on Benign Tertian Malaria. 6. On Heterologous Tolerance.**—*Amer. Jl. Hyg.* 1934. Sept. Vol. 20. No. 2. pp. 482–487.

An attack of malaria establishes some degree of tolerance of infections with heterologous strains. This tolerance is not sufficiently great to deal with a heterologous strain as efficiently as it can with the homologous strain, but it is capable nevertheless of diminishing the severity

of the heterologous illness. The authors reached this conclusion as the result of observations made on two groups of persons submitted to therapeutic inoculation with malaria. The first group contained people who had previously suffered from malaria, the second group contained people who had not. In the first group, the incubation period was longer, the fever was lower, and the loss of haemoglobin (from the beginning to the end of a 30-day period) was less. The same held good in a small group inoculated first with one strain, and then with another after they had recovered from the effects of the first. *W. F.*

Boyd (Mark F.) & Stratman-Thomas (Warren K.). **Studies on Benign Tertian Malaria. 7. Some Observations on Inoculation and Onset.** —*Amer. Jl. Hyg.* 1934. Sept. Vol. 20. No. 2. pp. 488–495

Schaudinn's statement that sporozoites enter erythrocytes is disputed.

Excision of the bite a few minutes after the application of an infected mosquito did not prevent infection, and the authors conclude that sporozoites must therefore be injected directly into the blood-stream.

Sporozoites can gain access to the blood vessels by penetrating the tissue, as was shown by applying infected mosquitoes to a blister raised by cantharides.

Schaudinn stated that he had observed the entry of sporozoites into erythrocytes, and their transformation into trophozoites. This observation has never been confirmed. A patient, "B," under the authors' care, was bitten by 15 heavily infected mosquitoes; on the same day and on each of the succeeding 9 days 10 cc. of his blood was inoculated into a series of susceptible persons. None of the series inoculated before the 9th day became infected, those inoculated on the 9th, 10th and 11th days became infected, and parasites appeared in the blood of patient "B" himself on the 11th day. "Despite the heavy inoculation given patient 'B,' parasites . . . could not be detected earlier than the 8th day following inoculation. This does not support the view that sporozoites invade the erythrocytes and thus directly initiate schizogony."

It is sometimes desirable to distinguish between a primary attack of malaria and a recurrence. In areas of low endemicity, the authors have found that the onset of a recurrence is distinguished from the onset of a primary attack by a greater number of parasites and a palpable spleen, but, where there is a great deal of malaria and more than one strain of parasites, these criteria are not very helpful. As regards the onset of the attack: in 37 per cent. parasites were found before the fever; in 37 per cent. fever occurred before the parasites, and in 26 per cent. both parasites and fever appeared on the same day.

W. F.

Helpern (Milton). **Epidemic of Fatal Estivo-Autumnal Malaria among Drug Addicts in New York City transmitted by Common Use of Hypodermic Syringe.**—*Amer. Jl. Surgery.* 1934. Oct. Vol. 26. No. 1. pp. 111–123, 142. With 6 figs. [26 refs.]

During the five months from September 25, 1933, to February 28, 1934, there occurred in New York 49 cases of malaria among drug addicts who were intravenous injectors of heroin; 39 were subtertian infections, 21 of which were fatal; 9 were quartan, 1 of which was fatal;

1 was benign tertian. At this time of year malaria does not ordinarily occur and anopheles are almost non-existent in Manhattan, the district in which the men lived. It was found on enquiry that the infection had been transmitted by the hypodermic syringe which was commonly shared by several addicts. A photograph of the " works " is given ; this includes the improvised syringe and the bottle-cap in which the solution was prepared. Other photographs show sections of the cerebral cortex from a fatal case, with dilated capillary vessels containing red blood cells heavily infected with parasites. [See this *Bulletin* p. 109 above for references.] *W. F.*

Sautet (J.) & Cordoliani (S.). Fièvre ondulante et paludisme. Difficulté du diagnostic au moment des poussées épidémiques. [**The Diagnosis between Undulant Fever and Malaria.**]—*Bull. Soc. Path. Exot.* 1934. Oct. 10. Vol. 27. No. 8. pp. 719–723.

Undulant fever and malaria are both endemic in Corsica, and the spring epidemic of undulant fever coincides with the spring epidemic of benign tertian. The following points are of assistance in making a diagnosis : malaria is commoner in young children, undulant fever is commoner in adults ; undulant fever may occur anywhere, malaria is limited to certain parts of the island ; undulant fever does not react to quinine, malaria does react. The examination of blood-films and sera is the only means of making a sound diagnosis. *W. F.*

i. Mühlens (Peter). ii. Schlesinger (Wilhelm). Kommen heute noch Kriegsmalariafolgen vor ? [**Are the Sequelae of War Malaria still Occurring ?**]—*Arch. f. Schiffs- u. Trop. Hyg.* 1935. Feb. Vol. 39. No. 2. pp. 74–76. *Wien. Klin. Woch.* 1935. Mar. 22. Vol. 48. No. 12. p. 365.

i. After reference to numerous diagnoses of war malaria, and deaths in consequence, which have been reported in the last two years in Germany the author notes that in such cases examined during the last 6–8 years at the Hamburg Tropical Institute malarial parasites have not in one single instance been found even after provocative methods and the like. Such reports should be critically received and no case accepted as malaria unless the parasites have been identified or confirmed, or in the case of death the organs examined by a competent person. He wishes such material sent to the Tropical Institute at Hamburg.

ii. From time to time Schlesinger gets war patients complaining of rigor with fever and terminal sweating but in the last ten years he has never found malarial parasites nor pigment in the blood nor mononucleosis, nor appreciable splenic enlargement. In 1920, in the great epidemic of influenza, he noticed that old malarials with pneumonia responded with intermittent fever though parasites were not demonstrable. He suggests that in these instances the heat centre has become adapted to that type of response and so would explain the rigors of his war patients, which have thus no special significance. *A. G. B.*

Alberto Videla (Carlos). Reactivación del paludismo latente por el cloruro de calcio. [**Reactivation of Latent Malaria by Calcium Chloride.**]—*Prensa Méd. Argentina.* 1934. Dec. 12. Vol. 21. No. 50. pp. 2378–2380. [13 refs.]

The author compares the provocative effect of berberine sulphate, adrenalin, and chloride of calcium in latent malaria. He tested these on 20 subjects infected with simple or double tertian and simple quartan

malaria. The berberine salt given by mouth was ineffective in three cases, and, intravenously, failed in another three. Adrenalin injected intramuscularly for several days in a dose of ½ to 1 cc. of a 1/1,000 solution failed in 11 cases. Chloride of calcium, daily doses 10 cc. of a 10 per cent. solution intravenously, gave a positive result in four of the six patients in whom the other drugs had failed. The parasites appeared by the second or third day, and this reappearance coincided with a positive Henry's ferroflocculation and enlargement of the spleen [see this *Bulletin*, Vol. 28, p. 595]. *H. H. S.*

MANSON-BAHR (Philip). **The Prognosis in Malaria Infection.**—*Lancet.* 1934. Dec. 1. pp. 1237–1238.

Relapses in subtertian malaria can be entirely prevented by atebrin.

This excellent article should be read in full ; only a few points can be dealt with here. Dr. Manson-Bahr holds the view of most workers in the tropics that " In all forms of malaria, as in other protozoal infections, the earlier and the more energetic the treatment, the greater the hope of effecting a permanent cure." Not everyone will agree with him when he says " Apart from its disagreeable habit of manifesting relapses at odd and often unexpected intervals, benign tertian malaria cannot in any sense be regarded as a menace to life." He puts the life span of the benign tertian parasite at 3 or, at the most, 3¼ years, that of subtertian at about 9 months, and that of quartan at anything up to 5 or 6 years. He points out that the parasites of subtertian malaria have acquired the property of lying low and of springing into activity, precipitating sudden catastrophes, even death, by accumulating in the capillaries of the internal organs, so producing acute pancreatitis, dysentery, cerebral attacks, malarial amblyopia (a result of malarial infection of the retinal vessels) and many obscure symptoms. " These major and tragic aspects of subtertian malarial infections are more liable to be seen in the non-immune person—*i.e.*, the tenderfoot on his first visit to a malarious country."

Blackwater fever, on the contrary, seldom develops during a first infection ; the longer a person is infected, the more liable is he to develop it. It is the worst feature in the prognosis of subtertian malaria, for the mortality of the disease is about 25 per cent. It may appear at any time from the day of arrival in England up to 9 months after arrival, when the liability disappears. Attention is drawn to certain mental conditions which may resemble encephalitis lethargica, and " are produced by small subcortical haemorrhages which, if not immediately fatal, leave behind them disseminated malarial granulomata which represent the organization of the minute haemorrhages." The author considers that " it is now possible to exterminate this parasite [subtertian] in the blood with adequate doses of atebrin, with quinine perhaps as an adjunct, in a way never formerly anticipated ; it is possible to prevent entirely the recurrence of relapses." *W. F.*

DE SILVA (Stanley). **The Stroke in Malaria.**—*Jl. Trop. Med. & Hyg.* 1934. June 1. Vol. 37. No. 11. pp. 166–167.

A person who has once had cerebral malaria never has it again.

By " the stroke " the author means an attack of cerebral malaria with loss of consciousness, due to infection with malignant tertian parasites. He states that a patient with cerebral malaria either dies in coma, or

recovers and is free from further attacks of a similar nature. He himself has never met with a case in which there was a history of former " strokes," or in which subsequent strokes occurred. *W. F.*

VAN DER HORST (G. A.) & VERHAART (W. J. C.). Die Veränderungen im Gehirn bei Malaria. [**Cerebral Changes in Malaria.**]—*Virchows Arch. f. Path. Anat. u. Physiol.* 1934. Vol. 292. No. 4. pp. 417–427. With 4 figs. [43 refs.]

A study of the pathological anatomy of the brain in 21 cases of malaria in Batavia.

As a result of their investigations the authors found that the cases fell into different groups :—1. Cases with focal changes. 2. Cases with general changes and a few perivascular haemorrhages. 3. Cases with slight general changes, and 4. Cases without definite histological alteration of the brain, although pigment was present in the vessels. In the first group there were 8 cases and they all showed a lesion which was essentially the same as Dürck's granuloma ; it consisted of a perivascular necrosis surrounded by a number of microglial cells. This lesion is found in other diseases, and is, therefore, not specific for malaria.

From the investigation the authors conclude that pure malarial encephalopathy is extremely rare ; in 21 cases of malaria with cerebral changes it was only once found ; in the rest of the cases the clinical picture was obscured by cachexia, severe anaemia, jaundice and other complications ; it was the latter which caused death. Therefore the so-called malarial coma cannot be recognized as a special disease, the general intoxication playing the chief part. *E. D. W. Greig.*

RUGE (H.). Leberfunktion bei frischer Malaria. [**Liver Function in Acute Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. Jan. Vol. 39. No. 1. pp. 14–19.

A study of the changes in the blood chemistry in a series of cases of acute malaria with a view to testing liver function.

The author notes that most liver function tests have been made in old and chronic cases of malaria. With the object of supplementing our knowledge he investigated two cases of natural malaria, two cases artificially infected by mosquitoes and nineteen cases of inoculated malaria, all showing acute symptoms and infected with *Plasmodium vivax*. The blood sugar was estimated after administration of 40 grams lactose.

As a result of his observations the author concludes that the disturbance of the liver function in acute malaria increases as the attack proceeds. The damage is shown by the rise of the blood sugar curve after administration of lactose to over 30 mgm. per cent., the increase of the nonprotein nitrogen, the occurrence of an indirect positive van den Bergh reaction. Under treatment with atebrin the changes in the blood chemistry returned to normal limits. *E. D. W. Greig.*

VAN NITSEN (R.). Quatre observations de paludisme congénital. [**Four Cases of Congenital Malaria.**]—*Bull. Méd. du Katanga.* 1934. Vol. 11. No. 3. pp. 83, 85–87.

LAFFONT has proposed to limit the term " congenital malaria " to those cases where parasites are found at birth, and to designate as " hereditary malaria " the cases in which the infection is acquired during the delivery and where the parasites appear several days later.

Two of the author's cases come in the first category : in one, parasites were found in large numbers on the second day, and in the other on the third day. The other two cases were free from parasites until the tenth day. *W. F.*

Moshkovsky (S.) & Poliakova (A.). Sur une méthode d'évaluation chimio-thérapeutique des propriétés schizotropes des préparations antipaludiques. [**A Method for Testing the Schizotropic Properties of Antimalarial Drugs in Chemotherapeutic Experiments.**]—*Med. Parasit. & Parasitic Dis.* Moscow. 1934. Vol. 3. No. 5. [In Russian pp. 395–400. French summary p. 400.]

The authors propose to test the " schizotropic " efficacy of anti-malarial drugs, *i.e.*, their damaging power upon schizonts, by determining the minimal single dose capable of producing an appreciable retardation in the course of the infection. This dose, named *dosis affectans*, differs from the " minimal effective dose " in that it does not lead to the disappearance—even temporary—of the parasites, but only lowers their growth-curve.

In determining this dose a number of birds (the authors employed linnets and siskins) are infected with equal quantities of parasites (*Plasmodium praecox*) capable of producing acute lethal infections without treatment. Those birds which show an equal percentage of infected erythrocytes at a given moment are selected for the comparative tests, for which atebrin and plasmochin were used. The minimal doses of these preparations producing the earliest diminution in the number of parasites constituted the *dosis affectans*. This proved to be between 0·2 and 0·3 mgm. per 20 gm. body-weight in the case of atebrin, and 0·03 to 0·04 mgm. for plasmochin. The ratio of D.A. of these two preparations corresponds more or less closely to that of their respective curative doses in human malaria. *C. A. Hoare.*

Moshkovsky (S.) & Burova (L.). **Method of Evaluation of the Gametotropic Properties of Antimalarial Drugs.**—*Med. Parasit. & Parasitic Dis.* Moscow. 1934. Vol. 3. No. 6. [In Russian pp. 445–451.]

The authors describe a method for testing the so-called " gamostatic " properties of anti-malarial drugs, *i.e.*, their inhibitory effect upon the sexual development of the malarial parasite, which renders it non-infective to the mosquito. The " gamostatic " effect manifests itself in an interruption of the process of microgamete formation and can be evaluated by observing the " exflagellation " of the parasites *in vitro*.

The tests were conducted with linnets and siskins experimentally infected with *Plasmodium relictum*, with linnets naturally infected with Haemoproteus and with human malarial parasites, using the following technique. Equal volumes of 1½ per cent. sodium citrate and infected blood are taken up in Pasteur's pipette and mixed on a slide. A small drop of the mixture is transferred to a fragment of cover-slip, measuring about 3–4 mm., over which a whole cover-slip is placed. This is mounted upon Ranvier's ring attached to a slide or over a hollow slide, with 1–2 drops of water at the bottom of the moist chamber, which is sealed with vaseline. Observations were made under a microscope placed together with the moist-chamber in a box kept at 28–30°C. Under these conditions exflagellation in Haemoproteus

occurred 3–8 minutes after the blood was taken, in *Plasmodium relictum* after 13–15 min. and in *P. falciparum* after 3–5 min. The effect of drugs upon exflagellation was tested with plasmochin, plasmocide, atebrin and quinine.

In the case of plasmochin and plasmocide a dose of 0·1 mgm. and 0·09–0·12 gm. respectively per 20 gm. of body weight, injected into birds infected with Haemoproteus, stopped exflagellation in 24 hours. On the other hand, 1 to 5 injections of 0·88 mgm. atebrin administered together with 2 mgm. of quinine per 20 gm. body-weight, had no effect upon the microgametes after 24 hours and more (only about 7 injections of atebrin inhibited exflagellation).

The experiments on *P. falciparum* were conducted with plasmocide and atebrin. The minimum dose of plasmocide producing cessation of exflagellation in 24 hours proved to be 0·09 gm. (given in three tablets on one day), while continued daily treatment up to 8 days caused the disappearance of the gametes from the blood. As in the case of bird-malaria, atebrin administered in doses of 0·12 gm. three times a day in the course of 5–8 days failed entirely to stop exflagellation. The authors recommend this method of testing the inhibitory effect of anti-malarial drugs upon exflagellation for general use in experimental chemotherapy of malaria. *C. A. Hoare.*

Kritschewski (I. L.) & Demidowa (L. W.). Ueber eine noch unbekannte Funktion des retikuloendothelialen Systems. XXII. Ueber die Bedeutung des retikuloendothelialen Systems in der Therapie der Malaria. [**The Significance of the Reticuloendothelial System in the Treatment of Malaria.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1934. Dec. 31. Vol. 84. No. 1. pp. 14–21. With 2 figs.

An investigation to determine the effect on the therapeutic activity of antimalarial drugs of blocking the reticuloendothelial system.

The drugs studied by the authors were quinine, plasmoquine, derivatives of acridine and acrichin No. 8. For the tests he employed birds infected experimentally with *Plasmodium praecox*. It was essential to determine very accurately the limit of the therapeutic dose of each drug for the birds. In one series of experiments the RES was blocked with trypan blue, in the other series the RES was intact. As a result of the investigation the authors reach the conclusion that the therapeutic activity of antimalarial drugs (quinine, plasmoquine, derivatives of acridine and acrichin No. 8) is greatly lowered by blocking the RES with trypan blue. *E. D. W. Greig.*

Quarterly Bulletin of the Health Organisation, League of Nations. Geneva. 1934. Sept. Vol. 3. No. 3. pp. 325–358. With 2 graphs.—**The Therapeutic Efficacy of Totaquina in Human Malaria. I. Clinical Tests carried out under the Auspices of the Malaria Commission** [Pampana (E. J.)]. **II. Critical Analysis of the Results Achieved** [Fletcher (William)].

Totaquina acts like quinine as a potent remedy in all forms of malaria.

Tests of different samples of Totaquina (see this *Bulletin*, Vol. 29, p. 461, and p. 114, above) were carried out during the malaria season of 1933 in Algeria, Bulgaria, China, France, Italy, the Federated Malay States, Morocco, Rumania and Spain. Special cards for recording the

results were drawn up and sent to all the observers. The present report covers a total number of 1,144 cases, comprising 1,055 treated by totaquina and 89 treated by quinine as controls. Five samples of totaquina were used in these tests, they were as follows :—

Type I (made direct from the bark of *Cinchona succirubra*).
1. Made by Messrs. Burroughs & Wellcome.
2. ,, Madras Government Factory.

Type II (made from residues of quinine extraction and adjusted to the Malaria Commission's standard specification).
3. Made by Turin State Quinine Factory.
4 ,, ,, ,, ,, ,, ,,
5. Made by Messrs. Howards, London.

An analysis of these is given in the report. One of the Type II samples, number 4 above, resembled the Type I totaquinas in the proportions of the various alkaloids ; the other two, number 3 and 5, contained less quinine and more cinchonine, according to analyses made at the Wellcome Chemical Research Laboratories. The tablets of number 3 did not disintegrate very readily in water, because they were composed of pure totaquina without the addition of any substance to render them friable. Compressed tablets similarly manufactured, but made up with an excipient designed to render them friable, break up easily and can be kept for long periods under tropical conditions without special precautions.

A feature brought out by a study of the records was the difference in the condition of the patients at the beginning of treatment in one centre and in another. In some places the patients' symptoms were much more severe than in others. Another striking difference was the response of the patients to treatment : this was noticeably more prompt in the Rumanian centres than elsewhere. Neither the same samples of totaquina nor the same doses were used at all the different centres. This lack of uniformity would have mattered less if a control series had been treated with quinine at each centre ; unfortunately this was done only in Rumania and the Federated Malay States. As regards toxicity, the case records contained no cogent evidence that totaquina was more toxic than quinine in the doses given.

" To sum up, the records of the cases treated at the different centres show clearly that Totaquina acts like quinine as a potent remedy in all forms of malaria ; but it must be remembered that a field trial of this kind is not a carefully controlled experiment and, when it comes to deciding whether Totaquina is a little better than quinine or not quite so good, one is on less sure ground and, in the absence of adequate controls treated with quinine, the yard-stick needed for more exact measurements is lacking. Similarly, the observations made at the different centres were not sufficiently precise and unanimous to warrant a final decision on the relative merits of the different samples of Totaquina." *W. F.*

Slatineanu (A.), Ciuca (M.), Balteanu (I.), Alexa (E.), Alexa (I.), Francke (M.) & Rugina (I.). Efficacité thérapeutique des alcaloïdes totaux de l'ecorce de quinquina dans le paludisme humain (infection naturelle). [**The Efficacy of the Total Alkaloids of Quinine Bark.**]—*Bull. Soc. Path. Exot.* 1934. Oct. 10. Vol. 27. No. 8. pp. 723–728.

From a study of 441 cases of malaria treated comparatively with different samples of totaquina and with quinine, the authors concluded that the samples used were as efficacious as quinine when the content

of crystallizable alkaloids and of quinine were the same as those of totaquina Type I; but that those Type II products in which the quinine was much less and the cinchonine much higher, were less efficacious unless given in larger doses. *W. F.*

CHOPRA (R. N.), ROY (A. C.) & GUPTA (B. M. Das). **On the Concentration of Quinine in the Blood after Intravenous and Intramuscular Injections.**—*Indian Med. Gaz.* 1934. Oct. Vol. 69. No. 10. pp. 561–566. With 2 figs. [17 refs.]

There is little difference in the concentration of quinine no matter by what route it is administered. Parenteral injections should not be used for routine treatment.

Six monkeys were inoculated intravenously, and six intramuscularly, with quinine acid hydrobromide. The amount of quinine in the blood was estimated at intervals. The resulting average concentration of quinine in the blood was as follows :—

	Hours after injection of quinine.						
	¼	½	1	2	4	5	24
Concentration after intravenous	1·37	1·27	1·05	0·63	0·35	0·36	0·00
Concentration after intramuscular	1·37	1·36	1·04	0·83	0·62	0·64	0·32

It is clear from this table that there is " not any marked difference in the concentration of quinine attained in the blood at different intervals of time when the effect of its administration by the two routes, *i.e.*, intravenous and intramuscular is compared." The maximum concentration in the blood was attained in 15 minutes by both methods. It has been stated that after intramuscular injection much of the quinine remains unabsorbed in the muscle. The authors investigated this in rabbits, and found that only small proportions remained unabsorbed after 20 hours. Four human patients were given quinine by the mouth, and also by intravenous and intramuscular inoculation.

The authors found that " if allowance is made for small variations due to the constantly changing factors in the animal organism, the concentration of quinine in the blood after administration by the oral and parenteral routes runs almost parallel. In some cases the concentration obtained within the first few hours after oral administration was definitely smaller, but the concentration soon rose to practically the level of the parenteral routes. . . . The oral route is undoubtedly the method of choice in the vast majority of patients . . . even in cases of severe malaria complicated with dysentery quinine has been shown to be absorbed . . . parenteral injection . . . should not be used for routine treatment of malaria, but is specially indicated in acute cases of severe type for as long as the emergency lasts." *W. F.*

MURPHY (R. A.). **Quinine in the Therapeutics of Malaria.**—*Indian Med. Gaz.* 1934. Oct. Vol. 69. No. 10. pp. 566–567.

The author who has had many years' experience of the treatment of malaria in Assam pins his faith on a prolonged course of quinine. He

has been able to follow up his European patients for long periods. He treats the acute stage with 20 grains daily and then gives 10 grains a day for 3 months. The results in 110 cases were as follows :—cured, 80 ; relapsed, 20 ; unknown 10. Patients who had no fever for one year after treatment were counted as cured. He controls vomiting with adrenalin. He quarrels with the dictum of the Malaria Commission that, in relapses, it is safe to abstain for a day or two from giving a specific drug, and states that many a coolie child dies in convulsions just during these first few days of a relapse. [But it must be remembered that the Malaria Commission's report dealt with the subject " from the point of view of persons who are in a position to obtain expert medical advice and efficient care rather than from that of the mass of the population of malarious countries. The report does not contain information on plans for treating outpatients who attend at hospitals and dispensaries."] *W. F.*

WILLIAMSON (H.) & SINGH (Shamsher). **The Early Treatment of Malaria.**—*Indian Med. Gaz.* 1934. Oct. Vol. 69. No. 10. pp. 568–570.

The authors believe in intramuscular inoculations for the routine treatment of malaria (see CHOPRA, ROY and GUPTA above).

They have " recently been carrying out a series of experiments in treating a series of 600 cases of ' parasite positive ' benign malaria " ; and they conclude that " the dangers of intramuscular quinine have been exaggerated, and it is the best treatment for severe cases of benign malaria." Three hundred cases were given quinine by the mouth, 30 grains a day in a mixture ; mag. sulph., calomel, and sodium bicarbonate being given as well. [Where these barbarous mixtures are used, patients will naturally do all they can to avoid taking them. As the authors say, " one great advantage of injected quinine is that the attendant knows that the patient is getting what the doctor ordered."] One hundred and fifty cases were given intramuscular injections. No untoward results followed and the pain " has never been so severe as that commonly felt after antityphoid inoculations." No less than 150 of the 600 benign tertian cases were treated with intravenous injections, 5 or 10 grains in 5 cc. of normal saline. A reaction occurred in about 30 per cent. of the patients ; this consisted of rigors, collapse, vomiting and diarrhoea. One patient collapsed and died. Probably most people will agree with the authors that " it seems fair to assume that these reactions are due to the method and not to the drug." They naïvely quote a remark made by one of their colleagues in Quetta, " If I give an intravenous quinine I often find another doctor in attendance next time I go to see the patient." [Quinine, a gift of the gods, is loathed and feared ; this is not difficult to understand.]

W. F.

SUBRAHMANYAM (S.). **Intravenous Quinine Therapy in Malaria.**—*Indian Med. Gaz.* 1934. Oct. Vol. 69. No. 10. p. 570.

The author, who is attached to the Government Headquarters Hospital at Ootacamund had not had the alarming experience of WILLIAMSON and Shamser SINGH (see above), and he recommends intravenous injections for the routine treatment of malaria.

Since April 1932, about 300 cases of malaria of all types have been treated in the hospital, and the intravenous route has been almost invariably employed. The adult dose is 10 grains of the acid hydrochloride in 10 cc. of distilled water, and the injection is given once a day for 6 days. In patients with low blood-pressure, adrenalin is given at the same time. In cases where the blood-pressure begins to fall rapidly during the injection, or where there is respiratory embarrassment, the injection is stopped and is not repeated. In the majority of cases, there is a drop in the blood pressure of 5 to 15 mm. Hg., rarely 20 to 30 mm. The advantages of the treatment are : that it lasts only six days, it cuts short the primary attack, and it is at once cheap and effective. Almost every patient has complained of some giddiness and a slight burning sensation in the abdomen during the injection, but these are transient and need no treatment. In one or two instances, phlebitis has occurred, but it responded rapidly to treatment with two injections, intramuscularly on successive days, of 1 cc. of S.U.P. 36. Cyanosis and respiratory embarrassment were not observed, and the author concludes that " there does not seem to be any absolute contra-indication to the use of the drug intravenously." [It seems to the summarizer that to use intravenous quinine in every case of malaria is like using forceps in every case of labour.] *W. F.*

MANSON (D.). **Notes on Intravenous *versus* Intramuscular Quinine.**—*Indian Med. Gaz.* 1934. Oct. Vol. 69. No. 10. pp. 571–572.

The author does not hold the views of SUBRAHMANYAM (see above) with regard to the safety of intravenous injections. The main drawback is shock following the injection. " However competently the injection is carried out, this does occur, and in cases already in the stage of collapse, the onset of shock is very sudden and little can be done to check the inevitable sequel." He uses the intramuscular route with ever increasing confidence, and, even in cerebral cases, is in doubt about the advantages of intravenous quinine. *W. F.*

MANCA (Serafino). La permeabilità della barriera nervosa centrale alla chinina. [**The Permeability of the " Central Nervous Barrier " to Quinine.**]—*Riv. di Malariologia.* Sez. I. 1934. Vol. 13. No. 5. pp. 601–609. French summary.

Quinine reaches the cerebrospinal fluid ½ to 2 hours after administration.

The possibility of injected substances reaching the cerebrospinal fluid has been tested with a number of drugs—bromides, iodides, salicylates, arsenic, mercury, lead, morphine and several more—but, says the author, not the action of the " barrier " between the blood and the spinal fluid as regards quinine. For his experiments he used dogs and administered the drug intravenously, intramuscularly and orally. The usual doses were : for intravenous injection 20–25 cgm., for intramuscular 40–50 cgm., and *per os* 50 cgm. In all cases the quinine appeared in the cerebrospinal fluid after ½–2 hours according to the route of administration, quickest after the intravenous. The rate was enhanced if urotropine had been previously injected intravenously. Hence in severe forms of malaria, especially those with a cerebral symptom-complex, where circulatory disturbances obstruct the free

passage of quinine into the nervous system, the action of the drug can be assisted by preceding it with an intravenous injection of urotropine. Salicylate of sodium sometimes has the same effect as the urotropine.

H. H. S.

Lourie (E. M.). **Studies on Chemotherapy in Bird Malaria. II.—Observations bearing on the Mode of Action of Quinine.**—*Ann. Trop. Med. & Parasit.* 1934. Oct. 19. Vol. 28. No. 3. pp. 255–277. With 4 figs. [13 refs.]

Quinine does not act upon the parasites by setting in action the mechanism of immunity ; it appears probable that it may act directly.

These experiments were made with a strain of *P. cathemerium* producing 16 merozoites every 24 hours. It was found that a very precise synchronicity of development and sporulation could be elicited by exposing infected canaries to light from 6 a.m. to 6 p.m., and confining them in a dark chamber from 6 p.m. to 6 a.m. Sporulation was then at a maximum at 4 p.m. every day. When an infection was checked by giving a dose of quinine at 4 a.m. there was a profound interference with the asexual reproductive cycle. Growth of the parasites was retarded, there was delay in reproduction so that the peak was reached at midnight instead of at 4 p.m. ; the number of merozoites was reduced from 16 to about 6, and the characteristic synchronicity of development was entirely lost. These effects of quinine treatment are in striking contrast to the checking of a superinfection by the immune substances present in a latently infected bird. In the latter case there is a much more rapid disappearance of the parasites, but reproduction continues to be synchronous, the cycle is not delayed, and the normal number of merozoites is produced. " It must be quite clear, then . . . that the therapeutic effects of quinine cannot be attributed to an activation . . . of the machinery which ordinarily comes to the service, eventually, of an untreated infected bird. . . . The mode of therapeutic action would seem rather to consist in an assault by quinine, or a derivative thereof, upon the parasite itself. . . . It is suggested that the fact of malaria parasites being able to retain their viability in the face of *in vitro* exposure to quinine in strong concentration is not a sufficient argument against the direct action of unaltered quinine *in vivo*."

The author attempted to determine *in vitro* the concentrations which so affected the parasites that on introduction into a bird they exhibited a delay in growth and reproduction similar to that which occurs when quinine is administered to the host. These experiments were hampered by the fact that delay occurred in the subsequent *in vivo* growth and sporulation in the parasites of the control blood which was incubated without quinine. It was found that the concentration of quinine required *in vitro* to cause a subsequent delay in sporulation still greater than that of the control parasites, incubated in absence of the drug, was about 1 : 5,000, after an exposure of 1 to 2 hours at 39°C. " It is extremely unlikely, in view of the findings of other workers, that such very strong concentrations could be maintained for any length of time in the blood stream." Nevertheless minute amounts of quinine remain in the circulation for many hours after a therapeutic dose, and these very small amounts may be able, during that time, to act directly upon the parasites. An attempt was made to demonstrate the presence

of quinine, or an active derivative, in the blood, spleen or liver of birds which had received large doses of quinine, but the result was negative. [For No. 1 of this series see above, p. 117.] *W. F.*

Lourie (E. M.). **Studies on Chemotherapy in Bird Malaria. III.—Difference in Response to Quinine Treatment between Strains of *Plasmodium relictum* of Widely-Separated Geographical Origins.**—*Ann. Trop. Med. & Parasit.* 1934. Dec. 20. Vol. 28. No. 4. pp. 513–523. [12 refs.]

Different strains of bird malaria react differently to quinine.

The author demonstrates that in bird malaria response to quinine is liable to vary according to the particular distinct strain which may be under observation. Two strains of *P. relictum* were employed, one from America and the other from Germany. In the first series of experiments, canaries were inoculated with these strains and were treated with daily doses of quinine from the beginning. The quinine suppressed the infection in the canaries inoculated with the American strain, but it failed to do so in those infected with the German strain. Confirmation of these results was obtained in a second series of experiments where so large a dose of the infecting material was inoculated intravenously that parasites could be counted in the blood immediately afterwards. Quinine was given daily as before, with the result that the parasites of the American strain disappeared from the blood by the 10th day, but it had little or no effect upon the German strain. The two strains appeared to be of equal virulence ; the American strain was not milder than the German ; the difference was one of resistance to quinine. *W. F.*

Field (J. W.) & Kandiah (M.). **A Note on the Use of Mayer's Reagent for the Detection of Quinine in Alkaline Urine.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1935. Jan. 25. Vol. 28. No. 4. pp. 385–390. With 2 charts.

This is a further account of the work summarized in this *Bulletin* Vol. 31, p. 431, with reference to the failure of Mayer's reagent to precipitate quinine in alkaline solutions.

"We have now examined some thousands of specimens of urine for quinine using both Mayer's reagent and a modified Mayer's reagent containing acetic acid. For routine clinical use there has appeared little to choose between them. Their relative advantages and disadvantages have seemed to be as follows:—*Mayer's Reagent*: (1) Does not precipitate albumin within the normal clinical range of pH. (2) May fail to precipitate quinine from alkaline urine. *Acid Modification of Mayer's Reagent*: (1) Always precipitates albumin. (2) Always precipitates quinine if present in clinically significant amount. (3) Occasionally precipitates other substances. . . . While fully recognizing the limitations of any simple form of Mayer's test used in untreated urine, we believe the following procedures to be relatively free from fallacy :—

Using Mayer's Reagent:—

"(1) Add clear urine to each of two tubes.

"(2) To one tube add a few drops of glacial acetic acid.

"(3) To both tubes add a few drops of Mayer's reagent.

"i. If turbidity appears in both tubes, the presence of quinine is highly probable. Confirm by demonstrating the disappearance of the turbidity

on boiling the urine in the acid tube. If the turbidity does not disappear, albumin is probably also present. In this case, filter while hot to remove the albumin. The filtrate should be clear. Quinine, if present, will precipitate as the filtrate cools.

"ii. If both tubes remain clear, the presence of quinine at a concentration greater than 1/250,000 is highly improbable.

"iii. If the acid tube only shows turbidity, the presence of albumin, quinine, or both may be inferred. To identify quinine, boil and filter hot as in i." *W. F.*

NEWMAN (C. D.) & CHALAM (B. S.). **Atebrin in the Treatment of Malaria in Railway Employees.**—*Indian Med. Gaz.* 1935. Jan. Vol. 70. No. 1. pp. 5–8.

Atebrin is less expensive than quinine.

The patients were employees and their dependants on the Eastern Bengal Railway; 258 were given three tablets of atebrin daily for 5 days, followed by three tablets of plasmoquine daily for a further period of five days. A second series of 76 persons were given the plasmoquine and atebrin together during a single period of five days. In the first group 5·8 per cent. exhibited untoward or toxic symptoms but in the second group 21 per cent. The parasites disappeared after a few days treatment. The cost of treatment was on the whole less than treatment with quinine. (A three weeks course of quinine was taken for comparison.) *W. F.*

WILLIAMS (D. P.) & BHATTACHARYYA (Rasamay). **Notes on an Experiment on the Prophylactic and Curative Value of Atebrin and Plasmochin Therapy in a Tea Garden in Assam.**—*Indian Med. Gaz.* 1935. Jan. Vol. 70. No. 1. pp. 8–14.

Atebrin is more expensive than quinine.

"Atebrin is a more suitable drug for those who can afford it, but it cannot replace quinine in general use in a poor country like India."

The usual curative course of quinine on these tea gardens consists of 20 grains daily, for 7 days. The small reduction of malaria which followed prophylactic treatment with atebrin and plasmoquine was not sufficiently satisfactory to compensate for the expense incurred.

W. F.

KINGSBURY (A. Neave). **Psychoses in Cases of Malaria following Exhibition of Atebrin.**—*Lancet.* 1934. Nov. 3. pp. 979–982.

"Seven cases of psychosis following the exhibition of atebrin to cases of malaria have been collected. Five previously unpublished cases (McSwan) have been cited and five more cases are recorded. [There were apparently 12 cases in all, not 17.]

"These occurred among several thousand cases of malaria treated with atebrin. . . . The complication has been noted after a minimum of 6 tablets . . . a maximum of 21 tablets and an average of 13 tablets. The minimum interval between the commencement of treatment and the onset of symptoms was 1½ days, the maximum 12 days (5 days after the completion of the course) and the average 5½ days. The duration of symptoms in 8 mild cases varied from ½ to 7 days, with an average of 1½ days. Four more severe cases were referred to mental hospitals. . . . Two factors may be involved in the causation. The

action of atebrin *vis-à-vis* the malarial parasite may result in an intense liberation of ' toxins ' : on the other hand, atebrin (in lethal dosage) is known to have a toxic action on the central nervous system. Although the plasmodicidal effect of atebrin in a daily dosage of 0·2 grams is less favourable than that obtained with a larger intake, it is suggested that the risk of the development of psychoses would be minimised by caution in the selection of the daily dose." Details of 6 cases are given and on reading these one wonders how much was due to atebrin and how much was due to malaria. *W. F.*

DE LANGEN (C. D.) & STORM (C. J.). Experimenteel onderzoek van circulatiestoornissen door plasmochine en atebrine. [**Experimental Investigation of Circulatory Disturbances caused by Plasmoquine and Atebrin.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1934. Dec. 4. Vol. 74. No. 25. pp. 1646–1658. With 12 figs. [20 refs.]

Plasmoquine and atebrin are circulatory depressants in monkeys. Before putting out claims for the value of an antiparasitic medicament it is necessary to examine carefully into contra-indications and complications. In particular, investigation of its organotropic effects is very desirable and the determination of its therapeutic index, which is the ratio between the smallest effective dose and the smallest lethal dose for the infected individual. An advantage which the worker in the tropics has over those of other lands is the ease with which he can use monkeys as experimental animals, for they are animals from which results can be directly transferred to man. That plasmoquine and atebrin do affect the circulation adversely is apparent from their effect upon the blood pressure and the experiments recorded upon monkeys by the authors have reference to this as an index. Plasmoquine, in a quantity of 2 mgm. by intravenous injection (0·1 per cent. in physiological salt solution), causes on an average a fall of 500 mm. mercury and 1 cc. atebrin (2 per cent. solution) a systolic and diastolic fall of 100 to 65 mm. and 75 to 50 mm. respectively. The experimental results are illustrated throughout by very clear curve tracings. Some of the conclusions drawn are :—1. Plasmoquine and atebrin exert a depressing effect on the circulation in monkeys, especially by intravenous administration and cause disturbance of the respiration. These are only in part dependent on the speed of administration and the dilution. 2. It is possible then that intravenous injection, or a massive dose by the mouth, above all in malignant malaria where blood pressure is already low, may be followed by fatal collapse as well as by serious respiratory disturbance. 3. Adrenalin is recommended for intravenous injection along with plasmoquine and atebrin, as being in many respects antagonistic to them. 4. Adrenalin by its action on organs like the spleen, that are innervated by the splanchnic nervous system, brings parasites out into the peripheral circulation and so promotes contact between them and the anti-parasitic drug. 5. It is advantageous from the point of view of circulatory complications to combine quinine not only with plasmoquine but also with atebrin.*

W. F. Harvey.

* HUGHES finds that quinine given intravenously is a circulatory depressant and its administration not devoid of danger [this *Bulletin*, Vol. 28, p. 1006].—Ed.

Chopra (R. N.) & Chaudhuri (R. N.). **Some Observations on the Toxicity of Synthetic Anti-Malarial Remedies.**—*Indian Med. Gaz.* 1935. Jan. Vol. 70. No. 1. pp. 1–5. [17 refs.]

Points of distinction between blackwater and plasmoquine poisoning are given. Plasmoquine and atebrin should not be given together.

The authors give the details of a number of cases of poisoning in cases where a combined treatment with atebrin and plasmoquine had been given. They consider that combination with atebrin enhances the toxicity of plasmoquine. They state that though plasmoquine poisoning resembles blackwater fever, oxyhaemoglobinuria and oxyhaemoglobinaemia are never the result of the former though they are present in blackwater. Another point of distinction is the presence of cyanosis in plasmoquine poisoning and its absence in blackwater. They conclude "that 0·02 gram plasmoquine daily for a 2 or, at most, a 3 days' course causes disappearance of the crescents in the peripheral blood in cases of Indian strains of malaria and prolonged use is unnecessary and dangerous. Neither plasmoquine nor atebrin should be used for prolonged periods for prophylactic purpose. Patients should not be allowed to use these drugs except under direct medical supervision." *W. F.*

Tate (P.) & Vincent (M.). **The Action of Atebrin on Bird Malaria.**—*Parasitology.* 1934. Oct. Vol. 26. No. 4. pp. 523–530. [13 refs.

Atebrin does not act as a prophylactic in mosquito carried *P. relictum* infections in canaries.

The authors investigated the prophylactic action of atebrin in blood-inoculated, and in mosquito-induced, infections of *P. relictum* in canaries. They found that when the infection was conveyed by direct blood inoculation, atebrin acted as a clinical prophylactic and delayed the appearance of parasites; but when the infection was conveyed by mosquitoes it had no prophylactic action, whether it were given before or after the infective bites, though it diminished slightly the severity of the attack and the degree of splenic enlargement. In cases of infection by mosquitoes, parasites appeared in the blood during the course of atebrin treatment if this were prolonged beyond the normal incubation period. Asexual parasites which appeared in the blood of birds after atebrin treatment were devoid of pigment and stained badly. Atebrin treatment produced peculiar bodies in the blood cells of canaries.

W. F.

Kritschewski (I. L.), Magidson (O. J.). Halperin (E. P.) & Grigorowski (A. M.). Die Synthese chemotherapeutischer Verbindungen. Akridinderivate gegen Malaria. [**Synthetic Acridine Derivatives for the Treatment of Malaria.**]—*Giorn. di Batteriol. e Immunol.* 1934. Oct. Vol. 13. No. 4. pp. 685–700. English summary (9 lines).

The authors refer to the important investigations of Kikuth on atebrin, an acridine derivative, in the treatment of malaria (see this *Bulletin*, Vol. 29, p. 705, and Vol. 30, pp. 198 and 480), and then describe their own observations on the subject.

They employed birds infected with *Plasmodium praecox* using the method of Kritschewski and Sternberg for testing the therapeutic

activity of the drugs prepared by them. They studied in all nine acridine derivatives.

As a result of their investigations they found two acridine derivatives therapeutically active against malaria, namely, acrichin 5, which is the dichlorhydrate of the 2-methoxy-6-chloro-9-diethyl-amino-propyl-amino-acridine, and acrichin 8, which is the dichlorhydrate of the 2-methoxy-6-chloro-9-diethyl-amino-butyl-amino-acridine. The former has the same therapeutic index as atebrin and has the advantage of being easier to prepare. The latter has a higher index than atebrin and is also easier to prepare. *E. D. W. Greig.*

KIKUTH (W.) & SCHÖNHÖFER (F.). Das Plasmochin und Atebrin. [**Plasmochin and Atebrin.**]—*Muench. Med. Woch.* 1935. Feb. 21. Vol. 82. No. 8. pp. 304–308. With 5 figs.

An interesting account of the origin, trial and introduction of these two valuable synthetic antimalarial drugs. *A. G. B.*

MASSIAS (Ch.), BOURGIN (P.) & NGUYEN-VAN-TAN. Traitement du paludisme par un dérivé acridinique et un dérivé quinoléinique, nouvelles observations. [**The Treatment of Malaria with Acridine and Quinoline Derivatives.**]—*Bull. Soc. Path. Exot.* 1934. Dec. 12. Vol. 27. No. 10. pp. 929–932.

This concerns treatment with quinacrine followed immediately by a course of treatment with a mixture of rhodoquine and quinio-stovarsol known as stovoquine.

[Quinacrine is chloro-2-diethylamino-pentylamino-5-methoxy-7-acridine, or R.P.866 ; its action resembles that of atebrin (under which name it is now advertised) ; see this *Bulletin*, Vol. 31, p. 697.

Rhodoquine is dichlorhydrate of diethylamino-propylamino-methoxyquinoline, or Fourneau 710 ; its action resembles that of plasmoquine ; see this *Bulletin*, Vol. 30, pp. 479–850, and Vol. 31, p. 433. The name rhodoquine was formerly used for all the Fourneau quinoline derivatives, such as 574 and 915, it now indicates 710 only, the other products being distinguished by a letter following the name ; for example 574 is rhodoquine U.]

The authors' treatment was as follows : quinacrine 0·3 gram daily for 5 days, followed by 0·03 gram of rhodoquine and 0·75 gram of quiniostovarsol daily for a further period of 5 days. The above dose of rhodoquine is intended for a man of 60 kilos ; it should be calculated at the rate of 0·0005 gram per kilo of body weight. No toxic symptoms were produced by the treatment. The results as regards the disappearance of fever and parasites were excellent. *W. F.*

CHORINE (V.). Mécanisme et application de la réaction de Henry. [**The Mechanism of Henry's Reaction.**]—*Riv. di Malariologia.* Sez. I. 1934. Vol. 13. No. 6. pp. 807–822. With 2 figs. [48 refs.]

Flocculation with distilled water (surflocculance) and melano-flocculation are the same. Melano-flocculation is not due to specific antibodies.

Melano-flocculation, in therapeutic malaria, becomes positive about the third or fourth day after inoculation of the infection, and increases in intensity until the sixth or seventh malarial paroxysm. The

reaction becomes negative in one or two months under specific treatment. It disappears at the beginning of a paroxysm and returns as it passes off. The clinical value of the reaction is undeniable ; a negative reaction means the absence of malaria, but a positive reaction is only presumptive evidence of its presence. The flocculation of the serum in distilled water follows a curve parallel to that of its flocculation with melanine ; it increases with the malarial paroxysms, and it decreases under treatment in exactly the same way. The two flocculations are really the same, and the more simple reaction with distilled water, measured with the photometer, is to be preferred. Melano-flocculation is not due to specific antibodies ; neither the pigment of an ox's eye, nor that of a melanotic sarcoma possess antigenic power. The reaction is due, in the main, to an increase in the euglobulins of the blood, helped to some extent by an augmentation of the cholesterine and uric acid. The reaction is inhibited by an increase in the molecular concentration of the blood, and its disappearance during the malarial paroxysm is due to a rise in the salt content. Serum albumins and pseudoglobulins also tend to suppress the reaction. *W. F.*

Trensz (F.). Sur la nature des " fausses-floculations " en sérologie palustre. [**Henry's Reaction and the Nature of False Flocculation.**]—*C. R. Soc. Biol.* 1934. Vol. 117. No. 37. pp. 1106–1107.

Flocculation depends upon chemico-physical changes connected with the euglobulins.

Melano-flocculation occurs in several diseases in addition to malaria ; for example, it occurs sometimes in tuberculosis, syphilis, cirrhosis of the liver and anaemia, and in experimental trypanosomiasis it is very common ; in typhus exanthematicus and in the spirochaetosis of fowls it is almost always positive. Henry maintains that his melano-flocculation is a specific reaction due to the pigment antibodies. He considers that the flocculations which occur in these other diseases, where no pigment is produced, are of a different nature from those which occur in malaria, and he calls them " false flocculations." He has published a method by which, he claims, these " false flocculations " can be distinguished from the flocculations seen in malaria. (See above, p. 132.)

The author has employed this technique in the examination of 18 animals infected with trypanosomiasis, with the result that 4 were positive, 3 were doubtful, and 11 negative. These flocculations were therefore true flocculations. He concludes that there is no difference except in degree between the flocculation occurring in malaria and that occurring in other diseases, and that the phenomenon of flocculation depends upon physico-chemical change connected with the euglobulins of the serum. *W. F.*

Trensz (F.). Sur les caractères distinctifs entre la " floculation " et la " surfloculation " du sérum des paludéens. [**Henry's Reaction. The Distinction between Flocculation and Surflocculation.**]—*C. R. Soc. Biol.* 1935. Vol. 118. No. 1. pp. 11–12.

The author considers that the two phenomena are distinct from one another.

Surflocculation is due to the reaction which takes place between the euglobulins of the serum and distilled water ; flocculation is due to the reaction of these same euglobulins with melanine. If the melanine reaction is carried out in 0·3 per cent. ammonium chloride instead of water, surflocculation is suppressed while flocculation with melanine remains. (See Chorine below.) *W. F.*

Chorine (V.). Floculation du sérum dans l'eau distillée pure ou additionnée de mélanine. [**Henry's Reaction. Flocculation with Melanine, and in Distilled Water.**]—*C. R. Soc. Biol.* 1935. Vol. 118. No. 4. pp. 335–338. With 1 fig.

Melanine is merely an indicator, not an antigen.

Trensz (see above) states that surflocculation in distilled water and flocculation with melanine are distinct phenomena, and that surflocculation can be abolished by the addition of ammonium sulphate while flocculation with melanine remains unaffected. The author has plotted out curves of flocculation with melanine and with distilled water, as measured with the photometer, in different strengths of ammonium sulphate ranging from 1 to 10 per cent. The molecular salt diminishes the flocculation in both series, until, with increasing concentration, it is suppressed. The degree of flocculation in the melanine series is higher than in the distilled water series, and, consequently, visible flocculation disappears first in the latter (on the addition of about 3 per cent. ammonium sulphate) ; but the two curves are almost exactly parallel, and it is clear that melanine acts solely as an indicator. Henry employs sodium chloride in the same way as Trensz employs ammonium sulphate. *W. F.*

Castronuovo (G.) & Geracitano (A.). Le melanine e l'emozoina malarica. [**Melanin and Malarial Haemozoin.**]—*Riforma Med.* 1934. Dec. 1. Vol. 50. No. 48. pp. 1841–1845. With 3 figs. [14 refs.]

[This article is, at present at all events, mainly of academic interest.] By using the polarizing microscope the authors find that malarial pigment is not melanin. Melanin, they state, has its primary source in the nucleus of a cell and is the product of complex metabolic processes, katabolic and synthetic. In any case melanin is formed within the cell at the expense of protein derivatives and it is probable that its production is the result of the processes of condensation and oxidation due to complex enzyme action. Malarial pigment on the other hand is shown by crossed Nicol's prisms to be a substance of a crystalline nature which retains its doubly refractile characters after treatment with alcohol and fatty solvents and hence is not of a lipoid nature.

H. H. S.

Ghosh (B. N.) & Nath (M. C.). **The Chemical Composition of Malaria Pigment (Haemozoin).**—*Records of the Malaria Survey of India.* 1934. Sept. Vol. 4. No. 3. pp. 321–325.

"Haemozoin from blood heavily infected with *P. knowlesi* has been purified and subjected to a quantitative chemical analysis by micro-methods. Its carbon, hydrogen, and iron contents agree with those of haematin ; but compared with the latter pigment, the amount of nitrogen was found too low. This has been attributed to experimental error."

W. F.

Fróes (H. P.). Il " blu di metilene " nella diagnosi della malaria. [**Methylene Blue in the Diagnosis of Malaria.**]—*Riv. di Malariologia.* 1934. Vol. 13. No. 4. pp. 481–483. English summary (5 lines).

The author recommends the staining of thick films with an acid solution of methylene blue (methylene blue 1 gm., hydrochloric acid 0·5 cc., distilled water 90 cc., 90 per cent. alcohol 10 cc.). The stain is applied directly to the dry film and allowed to act 1–2 minutes, after which the slide is carefully washed in water till the film has a greenish-yellow colour. — *H. H. S.*

Eaton (Paul). **Susceptibility of Red Cells to Malaria. A Preliminary Note.**—*Amer. Jl. Trop. Med.* 1934. Sept. Vol. 14. No. 5. pp. 431–437. With 1 fig.

The author proposes the hypothesis that the red cell is susceptible to infection with malaria only when it is in the reticulocyte stage. He describes a method for staining reticulocytes.

The nucleus of the normoblast is extruded at the moment when the red cell is cast into the circulation. A network of fibrils which previously surrounded the nucleus remains for a short time, and, as this dissolves in the cytoplasm, the remaining fragments are drawn up into small spherical drops. The simplest method of staining these young cells, or reticulocytes, is to make a blood film on a slide which has been coated with a very thin film of brilliant cresyl blue. The serum dissolves the dye, the cells take it up while they are still alive, and the reticulum stains more deeply than the rest of the cell. The films may then be stained with Leishman's or Giemsa's stain. The average red cell lives about 30 days ; thus about 1/30 are destroyed and replaced by new cells every day. This means that 1/60 of the whole number of red cells (roughly 1·5 per cent.) are less than 12 hours old. The reticulocyte stage lasts about 12 hours, and it follows that the average percentage of reticulocytes in health is about 1·5. The author suggests that the infection of red cells occurs when they are in the reticulocyte stage. In a case of therapeutic benign tertian, 23 per cent. of the reticulocytes, and only 1·8 of the adult cells, contained parasites. In twenty additional preparations made from 4 cases, the percentage of infected reticulocytes ranged from 20 to 50. *W. F.*

Denecke (K.) & Malamos (B.). Ueber das makrozytäre Blutbild bei der Malaria. [**Macrocytic Blood Picture in Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. Feb. Vol. 39. No. 2. pp. 51–63. With 5 figs. [40 refs.]

A haematological study of cases of human and monkey malaria to determine if there is a macrocytosis of the red cells.

The authors conclude as a result of the investigation that 16 out of 24 cases of malignant tertian, and 6 out of 8 benign tertian, cases showed a macrocytosis (average diameter of red cells from 8·03 to 8·81 microns). The patients had a slight anaemia, as a rule, but at times the haemoglobin and red cell values were normal; marked anaemia was present in only one case. In monkeys infected with *Plasmodium knowlesi* an early macrocytosis occurred which could not be attributed only to a flooding with young large cells from the marrow. Eleven patients tested for liver

function showed that the liver efficiency was lowered, and this they considered as a possible cause of the macrocytosis. The blood picture was an early macrocytosis and never a megalocytosis. Bearing in mind this distinction between the red cells, it is possible that a proportion of the macrocytic red cells were not young marrow cells, which had been washed out, but red cells in the peripheral blood which had been altered in form by the action of toxic substances. *E. D. W. Greig.*

LOWE (John). **Studies in Untreated Malaria. Numerical Studies of the Parasites in Relation to the Fever.**—*Records of the Malaria Survey of India.* 1934. Sept. Vol. 4. No. 3. pp. 223–241. [19 refs.]

The relation of the numbers of parasites to the course of the fever is not the same in benign tertian and subtertian.

The parasite counts made by the author ranged from 20 to 202,000 per cubic millimetre. The highest recorded count found by him in the "literature" was one of 2,800,000 reported by CHOPRA, DAS GUPTA and SEN in a fatal case of subtertian.

In benign tertian malaria:—(*a*) A minimum count of 500 parasites per cmm. is usually necessary to cause fever, but this differs in different patients. (*b*) The variations in the numbers in a given patient are not due to migration of the mature parasites to the internal organs, but to their multiplication and destruction. (*c*) The schizont count, before a rigor, was compared with the young trophozoite count after the rigor. The largest increase in parasites was a ninefold one. Usually the increase is much less than this, because many of the merozoites—50 to 100 per cent.—fail to infect red cells and are destroyed. (*d*) On an average, only some 20 per cent. of the young trophozoites reach maturity, as was shown by counting them just after a rigor, and comparing the figure thus obtained with the number of schizonts present about 40 hours later.

In subtertian malaria:—(*a*) A count of 600 to 1,500 parasites is usually necessary to cause fever. (*b*) The wide and frequent fluctuations in their number is ascribed to the migration of mature parasites to the internal organs, and to the flooding of the blood with young parasites which come from these organs. (*c*) Increase or decrease in the parasite count is not necessarily followed by an increase or decrease in the fever of subtertian malaria, but, in benign tertian, the fever generally rises and falls with the number of parasites. The author considers that the destruction of parasites occurs in two ways: (1) by lysis or phagocytosis of free merozoites. (2) By ingestion of infected red cells by the reticulo-endothelial system. *W. F.*

TATE (P.) & VINCENT (M.). **The Susceptibility of Autogenous and Anautogenous Races of *Culex pipiens* to Infection with Avian Malaria** (*Plasmodium relictum*).—*Parasitology.* 1934. Oct. Vol. 26. No. 4. pp. 512–522. [18 refs.]

Two strains of the same species of avian malaria may produce very different infection rates in mosquitoes, and this difference is not merely one of the relative numbers of gametocytes formed by different strains.

An Algerian strain of *P. relictum* produced an infection rate of 89 per cent., while with a German strain the rate was only 43 per cent. The difference in the infection rates does not depend upon the strain of *C. pipiens* which is employed as a vector. A given strain of *P.*

relictum was transmitted to the same proportion of birds, by English, Greek, Maltese, Hungarian or cross-bred strains of *C. pipiens*. Some birds resisted infection with the sporozoites of *P. relictum*, and a few (less than 1 per cent.) resisted infection by blood inoculation. No seasonal influence was found as regards the infection of *C. pipiens* by *P. relictum*. *W. F.*

Shah (K. S.), Rozeboom (L. E.) & Del Rosario (F.). **Studies on the Infectivity of *Plasmodium cathemerium* of Canaries for Mosquitoes.** —*Amer. Jl. Hyg.* 1934. Sept. Vol. 20. No. 2. pp. 502–507.

Gametocytes and infectivity appear as early as trophozoites. Some individual mosquitoes are immune.

Canaries, *Culex pipiens* and *P. cathemerium*, were used in these experiments. It was found that when mosquitoes were fed on canaries during the early course of infection, some of them became infected during the first and second day on which parasites were present in the blood, but the percentage of infection was low. Individual immunity existed among mosquitoes ; when a batch of mosquitoes all ingested the same number of parasites, some of them resisted infection, provided the number was not too great ; when enormous numbers of parasites were ingested this individual resistance was broken down and all the mosquitoes became infected. It was found that mosquitoes feeding during the night were more likely to become infected than those feeding during the day, and the authors attribute this to the presence at night of a greater number of mature gametocytes in the blood. In infections of canaries, both with injections of blood containing asexual forms and with injections of sporozoites, gametocytes were produced early in the infection, and in most cases simultaneously with the appearance of asexual forms. *W. F.*

i. Taliaferro (William H.) & Taliaferro (Lucy Graves). **Morphology, Periodicity and Course of Infection of *Plasmodium brasilianum* in Panamanian Monkeys.**—*Amer. Jl. Hyg.* 1934. July. Vol. 20. No. 1. pp. 1–49. With 17 text figs. & 85 figs. on 2 plates. [21 refs.]

ii. —— & ——. **Alteration in the Time of Sporulation of *Plasmodium brasilianum* in Monkeys by Reversal of Light and Dark.**—*Ibid.* pp. 50–59. With 3 figs.

iii. —— & ——. **Superinfection and Protective Experiments with *Plasmodium brasilianum* in Monkeys.**—*Ibid.* pp. 60–72. With 2 figs. [15 refs.]

This investigation follows similar work on the infection of *P. cathemerium* in the canary (this *Bulletin*, Vol. 28, p. 494).

i. *Plasmodium brasilianum* was studied in 9 naturally infected and 67 experimentally infected Panamanian monkeys. These comprised black and red spider-monkeys, black and brown howlers, white-throats, marmosets and night monkeys. The sexual and asexual stages of the parasite are uniformly quartan-like. They do not enlarge the red cell. The asexual cycle exhibits a 72-hour quartan periodicity, and sporulation occurs regularly between 8 a.m. and 4 p.m. on every third day if one brood of parasites is present, but in natural infections there are often several broods in the blood. The mean number of nuclei occurring in sporulating forms varies between 8·5 and 10. The morphology of the parasite shows slight differences in the different

species of monkeys; in some, band forms are noticeably common; in others, the number of nuclei in the schizonts is above the average. Moreover, the disease is more severe in some species than in others. The infections are characterized by (1) an acute rise in the number of parasites; (2) a crisis with a fall in their number, either precipitous or gradual; (3) a developed infection which is of low grade; (4) a series of short latent-periods, when no parasites can be found, alternating with relapses. The relapsing nature of the infection corresponds to that of quartan malaria in man. Without any mortality of parasites, the infections should increase by about 9 times at each sporulation, since the number of merozoites produced is 8·5 to 10 for each schizont; but even during the acute rise, the greatest increase is far less than this. After the survivors successfully enter new cells, more perish during the acute rise, but an even greater mortality takes place at the crisis and thereafter.

"The death of the parasites before the crisis takes place in a previously uninfected host and represents natural resistance, that at and following the crisis is increased as a result of infection and represents acquired resistance." The authors found no difference between primary attacks and relapses; in both, the temperature was correlated with the growth of the parasites, and the fever was quartan in type unless several broods of parasites were present.

ii. By subjecting 3 monkeys infected with *P. brasilianum* to a reversal of the normal 12-hour periods of light and dark for from 21 to 43 days, the customary periodicity of the reproductive cycle was altered so that, within 2 to 3 weeks, sporulation occurred at a maximum rate just after 8 p.m., instead of just after 8 a.m. In one of the monkeys, the one brood of parasites present split into two broods, one of which sporulated 12 hours before, and the other 12 hours after, the original brood had sporulated.

iii. Monkeys with a latent infection of *P. brasilianum* proved immune to inoculations with the same strain and also to inoculations with the other strains tested. This immunity was effective immediately after the initial infection had abated and it lasted for at least a year (as long as tested). *W. F.*

Jerace (Felice). Osservazioni sui rapporti tra intensità dell'infezione, durata del periodo di incubazione, tipo febbrile e decorso clinico della malaria umana indotta con anofeli o con sangue. [**Intensity of Infection, Incubation Period, Type and Course of Inoculated Malaria.**]—*Riv. di Malariologia.* Sez. I. 1934. Vol. 13. No. 6. pp. 694–704. With 3 graphs. English summary (9 lines).

The author has studied the results of inoculating 52 general paralytics with malaria, 22 of them by mosquitoes and 30 by injection of blood from a patient with benign tertian parasites. The points for special observation were: (1) *The effect of the number of biting anopheles on the period of incubation.* He found that with up to ten anopheles the average incubation was 15·5 days, with more than eleven 13·7 days. Also with recently infected mosquitoes, up to ten days, the period was 14 days, with those infected earlier, from 11 to 30 days, the period was 16·5 days. The general average worked out as 14·5 days.

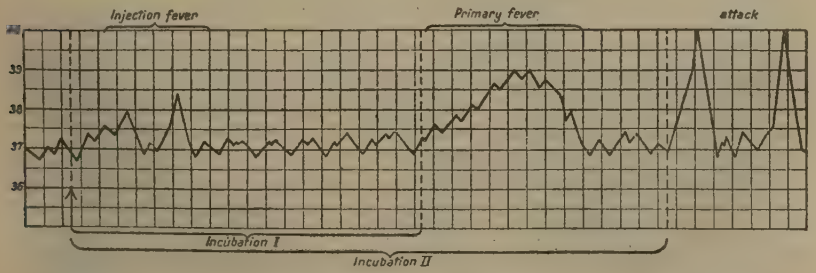
(2) *Comparison between mosquito infection and that by direct inoculation of blood* in the effects on incubation period, type of fever and duration of the acute fever, *i.e.*, number of febrile attacks. The incubation

period was on an average 12·5 days after blood inoculation, or two days shorter than that with mosquitoes. As regards the type of fever : after mosquito infection among the 22, fourteen or 63 per cent. had quotidian fever, 6 or 27 per cent. tertian fever and 2 or 9 per cent. a mixed type. In contrast, of the 30 inoculated with blood direct, 14 or 47 per cent. showed quotidian, 12 or 40 per cent. tertian, and 4 or 13 per cent. a mixed type of fever. Thirdly, as regards duration, in 27·3 per cent. (6 cases) only of those infected by mosquitoes did the fever come to an end spontaneously, *i.e.*, without the use of quinine, whereas in 13 of the direct blood infected or 43 per cent. this spontaneous cessation took place. *H. H. S.*

v. Assendelft (F.). **Therapeutic Malaria. A Parasitologic Study.**—*Riv. di Malariologia.* Sez. I. 1934. Vol. 13. No. 6. pp. 679–693. With 11 figs.

The primary fever which is usually tertian in the natural malaria of Holland is more often quotidian in therapeutic malaria.

These observations were made on 350 cases of benign tertian therapeutic malaria ; 288 were infected by means of subcutaneous injection, 32 by intravenous injection, 30 by mosquito bites. A fever which the author calls " injection fever " occurred during the first 3 days in 43 per cent. of the patients inoculated subcutaneously ; he attributes it to the multiplication of the parasites at the site of inoculation. When only a few parasites were inoculated, this fever did not arise ; when the number was over 10 million it occurred in 80 per cent., but when it was less than a million it did not occur at all. The length of the incubation period is influenced by the number of parasites injected, the compatibility of the blood of donor and recipient, relative immunity, etc. A fever occurs in primary infections at the end of the incubation period ; this lasts about a week and is known as the " primary fever" ; it is only slightly remittent. Primary fever does not often occur in patients who have had malaria before. The primary fever is followed by the attack which is of tertian type in the naturally acquired malaria of Holland, but is more often quotidian in therapeutic malaria where inoculations are made from patient to patient. The parasites have a tendency to form a second generation, and consequently two generations are often inoculated. The smallest number of parasites which is sufficient to cause fever, or the " pyrogenic limit," differs in different patients, and may be anything from 2 to 12,000 per cubic millimetre. *W. F.*



Normal fever curve in therapeutic malaria, showing injection fever (due to the development of parasites *loco injectionis*), primary fever and attacks.

[Reproduced from the *Rivista di Malariologia.*]

WHITE (R. Senior). **Three Years Mosquito Control Work in Calcutta.**—*Bull. Entom. Res.* 1934. Dec. Vol. 25. Pt. 4. pp. 551–596. With 10 figs. [72 refs.]

The number of kinds of mosquitoes known to occur in Calcutta is 46, and, although very few of these are of importance either economically or numerically, species which are vectors of malaria, filariasis, dengue and yellow fever are abundantly represented. Notes, chiefly concerned with bionomics, on all but two of the forty-six species are given. Those against which, owing to the numbers in which they are present or their importance as disease-carriers, work is required are :—*Anopheles subpictus, A. vagus, A. stephensi, Culex fatigans, C. vishnui, C. tritaeniorhynchus, C. gelidus, Aëdes aegypti* and *Aë. albopictus*. In addition, constant watch must be kept against the introduction of *Anopheles sundaicus*, " the notorious malaria-carrier of the Netherlands Indies and the Andamans."

The greatest pest in Calcutta is, however, *Culex fatigans*, to the bionomics of which, including a résumé of relevant literature from 1919 to 1934, the major portion of the present paper is devoted. In Garden Reach, in the third year of control, *C. fatigans* still formed " 65 per cent. of the total mosquito catch," and two-thirds of the specimens of this species caught annually are secured from January to April, when rainfall is low. Very little is yet known as to the exact breeding requirements of the insect, and investigation of breeding-places by specialists in the chemistry and bacteriology of sewage would probably yield valuable data. Meantime it is of interest to note that the open sewers to the east of Calcutta, stagnant or nearly so except at periods of heavy rain, are " simply enormous elongate breeding-places, where larvae can be spooned up at an almost unbelievable density."

Culex fatigans, of which the adults are on the wing in all stages, from newly emerged, unfed females to those which are ready to oviposit, appears to move about chiefly during the first two hours of darkness. In a controlled area it is possible, from the percentage of Stage I adults found in morning catches, to determine whether the control work is satisfactory. *E. E. Austen.*

COVELL (G.). **Note on the Control of Mosquitoes and Malaria in Delhi.**—*Records of the Malaria Survey of India.* 1934. Sept. Vol. 4. No. 3. pp. 273–289. [28 refs.]

The official policy in Delhi for the last 25 years has been to call for repeated reports and then to ignore the advice given.

The mosquito nuisance complained of in Delhi during April is entirely due to the prevalence of culicine mosquitoes, chiefly *Culex fatigans*. It has been suggested that the Kilokri Sewage Farm, situated at some distance from the town, is the source of these mosquitoes, but the author thinks it highly probable that most of the trouble is caused by local breeding in New Delhi itself. Expert advice on the control of mosquitoes and malaria in Delhi has been sought and given on many occasions during the last 25 years. For example Colonel SINTON has visited the city on four occasions, and has submitted three reports ; Dr. MACDONALD has made two visits and has also submitted a detailed report. Unfortunately only a small proportion of the permanent measures recommended has been carried out. For example : " Everyone of the many experts who have been called in to investigate malarial

conditions in Delhi has laid down that borrow-pits should be filled or drained, and that in future all excavations of this nature should be strictly prohibited. Yet during the last 3 years, fresh borrow-pits have been created as follows : . . . It is difficult to refrain from the comment that a community which allows this state of things after so many warnings deserves all the malaria and mosquito nuisance that it gets. . . . It is not considered that the control of mosquitoes and malaria in Delhi will ever be really satisfactory until a whole-time fully-trained malaria officer is appointed." The author understands, however, that the prospect of such an appointment being made is exceedingly remote. — *W. F.*

WILLIAMSON (K. B.). **The Control of Rural Malaria.**—Reprinted from *M.A.H.A. Magazine* [Malayan Agri-Horticultural Association]. 1933. July & Oct. Vol. 3. Nos. 3 & 4. pp. 145–150 ; 201–206 ; 1934. Jan. & Apr. Vol. 4. Nos. 1 & 2. pp. 224–228 ; 281–291.

The author advocates the use of rotting vegetation (Herbage Cover), metallic poisons, and sluicing to control mosquito breeding.

" The principles directing the control of malaria must accommodate themselves to two facts : firstly that the cost of effecting it by current urban procedures would be prohibitive, and secondly, that rural areas, with few exceptions, lie outside the possible range of skilled medical control." Some waters are rendered unsuitable by nature for the breeding of anopheline larvae, and the author's thesis is that these natural methods should be imitated and developed in order to free rural areas from malaria. The costs of ordinary subsoil drainage are prohibitive in such districts, except when money from general revenues is poured into small rural areas, as has been the case in Singapore and Penang. The waters of the coastal flat land of British Malaya are unsuitable for the breeding of the dangerous carrier *A. maculatus*. One of the main reasons for this is the presence of rotting vegetation, and this can be imitated by adding vegetable matter to the water of breeding places. " We can also regulate and multiply the sluicing effect seen in rapid streams after storms. Its effectiveness is probably the result of several things besides larvae being washed away." The larvae and eggs are stranded high and dry, the composition of the water is probably changed by the disturbance of the bed of the channel, and breeding ceases to occur. Oiling is unsuited for rural areas, not only because it is too expensive, but also because it kills crops and fish. Paris green, in Malaya, has been found dearer and less suitable than oil. There is no danger of arsenical poisoning from Paris green because a fungus, a Penicillium, causes it to be dissipated in the form of arseniuretted hydrogen, which does no harm in the open air though it has led to poisoning in rooms papered with wall-papers containing arsenical pigments. The possible effects of light and sound rays upon mosquitoes are discussed, but the author does not consider them likely to be of much practical value.

He has investigated the effect of slowly-dissolving mineral poisons upon larvae, and has found that the larvae of *A. maculatus* die within 5 days when copper or brass is present in the water. " The practical problem is to procure cheap ores or residues, slightly more soluble than most of the compounds tested in the laboratory, which will ensure that the minute traces of copper needed to safeguard breeding waters will be maintained in spite of rain and seepage flow ; and a search for these

is being made. Slow mineralization promises a possibility of effective control which may reduce the labour cost of treating pools and seepages to a fraction of what it now is. . . . But the method is clearly inapplicable to rapidly running water, and its usefulness in ponds and marshes is doubtful. On the other hand, the coppering of containers in towns threatened with yellow fever might be an invaluable aid in fighting the disease if it ever appears in this country." Another natural method is specially mentioned, it is known as " Herbage Cover."

" Shallow water up to a few inches deep is covered with plucked grass and herbage, or the leaves of trees . . . with a few twigs intermixed so as to form a brushwood drain for running water. The herbage is well trampled under foot until it forms an almost solid wall a foot or more in height . . . it cannot be penetrated by egg-laying mosquitoes ; it provides dense shade and, at least in stagnant water, sufficiently concentrated rotting to prevent the breeding of malarial species . . . very little dislocation of the herbage occurs in ordinary hillfoot or other drains, if their lower ends are provided with a double row of stakes to keep the solid mass of vegetation in position. . . . The method is particularly effective for stagnant pools where the biochemical effects of the rotting vegetation are greatest. . . . It is therefore probable that by this simplest, speediest, and cheapest of all anti-malarial measures, much of the malaria of the hills and hill valleys might be stamped out, if measures were taken to teach it to villagers. . . . To limit effort to oiling, which is better suited for dealing with the malaria . . . in other countries, is to disregard the help to be derived from local circumstances, and to fly in the face of reason and common sense. . . . Fish ponds should everywhere be established at the heads and along the course of the dangerous irrigation channels in hill rice valleys ; and should be used to sluice the channels."

[Sluicing has not proved satisfactory in other parts of the Malay States. *Ante*, p. 139.] *W. F.*

Morin (Henry G. S.). Note préliminaire sur un dispositif économique pour la destruction des larves d'anophèles dans certains ruisseaux. [**An Economical Method for the Destruction of Anopheline Larvae in Certain Streams.**]—*Bull. Soc. Méd.-Chirurg. Indochine.* 1934. Oct. Vol. 12. No. 8. pp. 743–746. With 3 figs.

The principal vectors of malaria in the highlands of Indo-China are stream-breeders, and when the rains come they are washed away by the flood. The author seeks to imitate this by artificial flushing. He has seen streams in Penang and in the Malay States which are treated with success in this way, thus saving the cost of oiling, etc. A barrage is built across the stream, and twice a week the impounded water is released by a coolie, and the stream is washed out. Diagrams are given of a siphonage apparatus designed by the author which would do this automatically.

[The difficulty in Malaya has been that the whole erection is washed away in the heavy rains. *Ante*, p. 139.] *W. F.*

Struthers (E. A.) & Sinha (S. N.). **The Use of Bamboo in Subsoil Drainage. Review of Three Years' Experiment.**—*Malayan Med. Jl.* 1934. Dec. Vol. 9. No. 4. pp. 197–199.

Bamboo pipes have been used for subsoil drainage in the Malayan town of Kuala Lipis for the last 3 years, and the authors conclude that this method is of use in isolated places where the cost of transport of oil or tile pipes is high, and where bamboos are plentiful.

The pipes are prepared by sawing through the stems on either side of the nodes and as close to the node as possible. They should have a diameter of not less than 3 ins. They are prepared by soaking in water in order to get rid of the internal pith coating. They are buried at least 5 ft. deep. The upper surface of the joints between the pipes is luted with clay in order to prevent the entrance of silt. Inspection pits made of tile pipes set vertically are put in at all junctions; the bamboo at the bottom of the pit is cut in half to form an open invert. [See this *Bulletin*, Vol. 31, p. 153.] *W. F.*

DE BENEDETTI (Augusto). Considerazioni tecnicopratiche sui metodi di lotta contro le larve anofeline. [**Measures against Anopheline Larvae.**]—*Riv. di Malariologia.* Sez. I. 1934. Vol. 13. No. 3. pp. 365–371. [10 refs.] English summary (5 lines).

The author discusses a method for causing Paris green to float for a long time.

In an earlier communication (this *Bulletin*, Vol. 31, p. 710, and *Riv. di Malariologia*, Vol. 12, pp. 92–97) the author described a method of mixing small quantities of mineral oil with ordinary garden soil, which was then heated and used as a diluent for Paris green. He now gives further details of his method of application and describes several experiments. In one, which was carried out in a bucket and not under field conditions, arsenic was discoverable chemically after 27 days, and though the quantity was very small, larvae were killed on that day within 24 hours.

[It seems that we have here an original idea, and it should surely be possible to discover more precisely how to render the soil and Paris green unsinkable and whether the Gutzeit test for arsenic is appropriate. It appears desirable that experiments should be carried out on several types of water in the field.] *P. A. Buxton.*

WASSILIEFF (A.). Expériences sur un nouveau produit arsenical larvicide. [**A New Arsenical Larvicide.**]—*Arch. Inst. Pasteur de Tunis.* 1934. Dec. Vol. 23. No. 4. pp. 449–454.

The copper arsenite prepared by the author is far cheaper than Paris green and equally efficient.

The drawbacks to Paris Green are its high price and the complicated machinery required for its manufacture. In order to be effective it must contain at least 50 per cent. of As_2O_3, and this makes it expensive. A preparation of arsenite of copper, known as "Arsmal," has been made in Russia (this *Bulletin*, Vol. 31, p. 57), it contains only 8·86 per cent. of As_2O_3, costs only a fifth of the price of Paris green, but is equally efficient as a larvicide. The author describes the method by which he has made copper arsenite from As_2O_3, $CuSO_4$ and $CaCO_3$. The results confirmed the work done in Russia. It was as effective as Paris green in destroying larvae under laboratory conditions, it was easy to prepare, and far less costly. The powder is finer than Paris green. *W. F.*

TREILLARD (M.). Destruction saisonnière domestique des anophèles adultes (*H. minima*) pour la prophylaxie antipaludique en Indochine méridionale. [**The Destruction of Adult Anopheles as an Anti-Malaria Measure in S. Indo-China.**]—*Bull. Soc. Path. Exot.* 1934. Dec. 12. Vol. 27. No. 10. pp. 937–939.

The author recommends an apparatus, similar to that employed in smoking out bees, for destroying anopheles in the coolies' huts on the

rubber-estates of South Indo-China. The fumigant is cresyl which drips slowly, from a reservoir, on to a hot-plate. The vapour is directed by bellows into all corners and crannies. This method is specially suited to *A. minimus* for it remains in habitations after feeding. It should be applied for several weeks before and after the rains. *W. F.*

RUSSELL (Paul F.). **Zooprophylaxis Failure. An Experiment in the Philippines.**—*Riv. di Malariologia.* Sez. I. 1934. Vol. 13. No. 5. pp. 610–616.

Zooprophylaxis is not only of doubtful value in the Philippines, but may actually be a danger. It has nowhere been shown to be an effective direct weapon against malaria. On alternate nights, the author tied up four buffaloes, one on each side of a native house at a distance of a few yards. Inside the house was a man under a mosquito net. The mosquitoes in the house were caught every 2 hours during the night for a period of two months. Many more anophelines were caught when the buffaloes were present than when they were absent. When an animal barrier was present, three times more anopheles were caught than on the nights when there was no barrier. *W. F.*

WILLIAMS (Louis L.), Jr. **Civil Works Administration Emergency Relief Administration Malaria Control Program in the South.**—*Amer. Jl. Pub. Health.* 1935. Jan. Vol. 25. No. 1. pp. 11–14.

Antimalaria drains have been dug by the Unemployed under the Relief Works Scheme.

The Federal Emergency Relief Administration was organized in the spring of 1933, and relief labour has been utilized for the control of malaria. The Public Health Service supplied the technical supervision for the drainage work and was given $350,000 by the Civil Works Administration. Nearly 6,000 miles of drains were cut which drained 100,000 acres of pond and more than 200,000 acres of swamp. The trend of malaria in the United States has been steadily downwards for the last 70 years, with a few slight interruptions ; one of these occurred in the summer of 1934, when there was more malaria than at any time during the last 20 years. It is encouraging to note that this increase in malaria has not affected those districts where Emergency Relief projects have been completed. *W. F.*

MOSNA (Ezio). La chinoplasmina usata nella profilassi della malaria. [**Quinoplasmine in Malaria Prophylaxis.**]—Reprinted from *Riv. "Croce Rossa".* Rome. 1934. Vol. 9. No. 6. 15 pp. With 5 graphs.

Administration twice weekly of quinoplasmine (2 cgm. to adults with doses proportionately less for children) to the entire population of 771 in a commune where malaria is hyperendemic, during a period of five months (18th May–21st October) has resulted in (1) a marked reduction in malaria incidence among the population in general ; (2) marked reduction in incidence among those born during the year ; (3) absence of infected anopheles throughout the period of experiment ; (4) absence of symptoms of toxicity or intolerance of the drug.

In 1931 MISSIROLI and MARINO treated the whole population of Torpè (East Sardinia) for a period of 10 days in April and June with quinoplasmine and adduced therefrom that the prophylaxis so obtained is of brief duration and that continued treatment of all patients with fever does not eliminate all sources of infection because many when first seen have gametocytes in their blood [see this *Bulletin*, Vol. 31, p. 473].

In the following year they treated the whole population on alternate days in June and July, the time of greatest prevalence of anopheles. As a consequence they found no infected anopheles during this period and that the time of maximum incidence of malaria was postponed to September. MISSIROLI and MARINO deduced that it would be possible to control, if not eradicate, malaria in hyperendemic zones by administration of this drug on alternate days throughout the time of malaria transmission. During the two months preceding the experiment described in this article examination of 191 children under 12 years living in Posada, on the east coast of Sardinia, 6 kilometres from Torpè, revealed a splenic index of 96 per cent. and a parasitic index of 48 per cent. The experiment consisted in administering quinoplasmine (quinine 0·3 gm. with plasmoquine 1 cgm.) twice weekly in doses of 2 cgm. to adults and correspondingly reduced doses to children, 0·25 cgm. to those under one year, 0·5 from 1–6 years, 1·0 from 6–12 years, 1·5 from 12–19 years. Administration was continued from 18th May to 21st October to 725 out of an entire population of 771. They were, for convenience, divided into three groups for treatment on different days. The only signs of intolerance were gastralgia (2 cases), giddiness and asthenia (6 cases). During the period careful search was made for all cases of malaria and any found was promply treated with quinine for 10 days in conjunction with plasmoquine twice a week.

Special points studied were: (1) the number of cases of malaria among the population; (2) the number among children born during the year; (3) the infection of anopheles; (4) the splenic and parasitic indices.

As regards the first, the inhabitants of the neighbouring Torpè, where quininization only was used, served as a control. The greatest number of cases occurred in August in both places, but whereas in Posada there were only 22 cases per 1,000 inhabitants, in Torpè there were 126, and during the whole period of observation there were 95 in the former and 276 in the latter, per thousand. The effect on gametocyte carriers is also worth noting. At Posada only two were found, one each with *P. vivax* and *P. falciparum*; at Torpè there were 44 with *P. vivax* gametocytes and 30 with those of *P. falciparum*.

The second point, the number of children born within the year attacked with malaria. In 1930 there were 14 attacked out of 49 or 48 per cent.; in 1931 and 1932 seven out of 30, or 23 per cent.; in the experimental period, 1933, only three out of 31 or under 10 per cent.

Thirdly, infection of anopheles. Of 816 caught in Posada in June-September not one was found infected, whereas among 572 caught in Torpè there were 10 or practically 2 per cent.

Fourthly, the splenic index in the successive years 1931–34, taken in March, has been 12·5, 5, 8·9 and 0·5 per cent. (in January 1930 it was 26·3), taking count of spleens enlarged to the umbilicus level; the percentages of non-palpable spleens have been 3, 6, 3·7 and 29·5 in the corresponding years. The parasitic indices from 1930–34 have been 42·2, 30, 32, 48 and 20 per cent. respectively. *H. H. S.*

Pikul (J.), Serguiev (P.) & Tibourskaya (N.). [**Experiment on the Prophylactic Use of Plasmocide in Daghestan with Observations on the Mosquito Infection Rate.**]—*Med. Parasit. & Parasitic Dis.* Moscow. 1934. Vol. 3. No. 4. [In Russian pp. 322–329. With 6 figs. [11 refs.]]

The greater part of this paper is devoted to an account of the result of treatment of the population of a restricted area with plasmocide. This was found to have a satisfactory schizontocidal and a marked gametocidal action in BT and MT (in the latter case it was combined with quinine). There was a diminution of the infection-rate in mosquitoes captured in the same area after mass treatment has been carried out. Prophylactic treatment with plasmocide is only briefly referred to : a group of 64 persons was treated with doses of 0·03 gm. administered two days in succession—followed by an interval of three days—but no protection resulted, since in 14 cases primary infections occurred during the period of treatment. *C. A. Hoare.*

Komp (W. H. W.) & Clark (H. C.). **A Third Year's Observation in Panama, with Special Reference to Control with Atabrine.**—*Amer. Jl. Trop. Med.* 1934. Sept. Vol. 14. No. 5. pp. 381–406. With 1 fig.

An adverse report on atebrin in the control of malaria. The danger of an oasis of malaria control in a region of high endemicity.

In August 1932, 24 cases of malaria among native Panamanians living along the Chagres River were treated with three 1½ grain tablets of atebrin daily for 5 days. Their bloods were examined monthly for 8 months, and, by the end of this period of observation, 19 of them had relapsed. In January 1933, a number of towns along the same river were surveyed, and the positive cases were treated with atebrin administered personally by the senior author. Each month, for a period of 8 months, these towns were revisited, and again those found positive were given a five-day course of atebrin. There were many relapses ; indeed the results in the atebrin treated towns were very little better than in a town where quinine was distributed by a native woman, and, as 5 days atebrin treatment costs about 2½ times as much as 5 days treatment with quinine, the authors conclude that " the use of atabrine does not seem to be a practicable method of malaria control under the conditions existing in certain native villages in Panama." Atebrin did not affect the power of crescents to infect mosquitoes ; abundant infection occurred in *A. albimanus* as the result of feeding upon atebrin-treated patients whose blood contained only crescents. As usual in work of this sort it was found impossible to treat all those found positive in the monthly surveys, because of their absence during the succeeding treatment period.

Though nearly every inhabitant of these river towns is infected with parasites, there is very little clinical malaria, and, during the past three years, the authors have not heard of a single death from malaria. " This of itself bespeaks a high tolerance for the disease." Certain persons were met with whose blood remained free from parasites for a year or more, and who then were attacked by clinically severe malaria. " It seems that the severity of clinical symptoms is greater in these 'primary' cases which occur after a long period of freedom than it is in cases which increase to clinical proportions from time to time in the course of a more or less continuous latent infection. This and similar

observations by other workers would lead us to believe that there is a certain element of danger in successful control of malaria to the inhabitants of any circumscribed area lying within a region of high endemicity. If continued freedom from parasites means a gradual loss of tolerance, the inhabitants of such an oasis may suffer severely from epidemics of malaria originating from introduced cases, so that their last state would be worse than their first." *W. F.*

Russell (Paul F.). **Avian Malaria Studies, IX. Atabrine as a Prophylactic Drug in Sporozoite Infections of Avian Malaria.**—*Philippine Jl. Sci.* 1934. Aug. Vol. 54. No. 4. pp. 483–493. [17 refs.]

Canaries were given intramuscular injections of atebrin for a few days, and were then inoculated with the sporozoites of *Plasmodium capistrani* from infected *Culex fatigans*. The atebrin did not act as a prophylactic against the sporozoites. It neither prevented infection nor lengthened the period of incubation. *W. F.*

Mehta (Dev Raj). **Studies on the Longevity of Some Indian Anophelines. Part I. Survival of** *Anopheles subpictus* **Grassi under Controlled Conditions of Temperature and Humidity.**—*Records of the Malaria Survey of India.* 1934. Sept. Vol. 4. No. 3. pp. 261–272. With 2 charts & 1 fig. [33 refs.]

A. rossii (*subpictus*) does not live long enough to act as a carrier in nature.

It has been suggested that the reason why *A. rossii* (*A. subpictus*) though easily infected in the laboratory is not a carrier in nature may be that it does not live long enough in the hot weather of the malaria season to allow the development of the parasites. These experiments were conducted at the Ross Field Experimental Station for Malaria at Karnal in order to test this hypothesis. The technique employed is described and illustrated. It was found that at 95°F., with humidity ranging from 30 to 90 per cent., *A. subpictus* lived from 3 to 8 days, and at 86°F. it lived from 6 to 14 days. "It is concluded that the females of *A. subpictus* live, for the most part, from 5 to 11 days at 30°C. (86°F.), and therefore the sporogonous cycle of the malarial parasite cannot be completed during the life of the mosquito host. This is one of the important factors elucidated to explain why *Anopheles rossii* (*subpictus*) is not a 'carrier' of malaria in nature."

W. F.

Bose (K.). **Larval Survey of the Land around Birnagar and Determination of the Longevity of the Local** *Anopheles culicifacies* **and its Habits.**—*Records of the Malaria Survey of India.* 1934. Sept. Vol. 4. No. 3. pp. 253–259. With 1 map.

A. culicifacies occurs here, but it is harmless. *A. philippinensis* is the carrier.

This survey was made under the auspices of the Birnagar Palli Mandali (Bengal). The results point to *A. philippinensis* as the principal carrier in the surrounding villages, as it is in Birnagar itself. The country round the town consists of rice-fields interspersed with villages. No *A. philippinensis* can be found in the rice-fields; here the

commonest species is *A. hyrcanus* var. *nigerrimus*. The chief breeding places of *A. philippinensis* are the ponds and lakes, known as bhils and tanks, which are overgrown with weeds. *A. culicifacies*, the notorious carrier of the Punjab and Southern India, breeds during the dry weather in the Churni River which flows past Birnagar; but during the rains and the fever season it becomes scarce. No infected specimens have been found in the district, and it appears to be unimportant.

W. F.

TOUMANOFF (C.). Observations sur les habitudes trophiques des anophélines de la colonie de Hong-Kong. [**The Trophic Habits of the Anopheles of Hong Kong Colony.**]—*Bull. Soc. Path. Exot.* 1934. Oct. 10. Vol. 27. No. 8. pp. 745–749. With 3 figs. on 2 plates.

A study of zoophily in the Far East.

In Shing-Mun, a temporary labour settlement, and Wo-Li-Hop, a small village, both situate in the colony of Hong Kong and with the same anopheline fauna, the percentage of naturally infected mosquitoes is very different. According to JACKSON, dissection of 2,155 *Anopheles minimus*, 10,936 *A. jeyporiensis*, 230 *A. maculatus*, and 2,818 *A. hyrcanus*, caught at Shing-Mun, showed 12·48, 9·93, 3·48 and 1·21 as the respective percentages of infection; at Wo-Li-Hop, among 1,185 *A. minimus*, 3,707 *A. jeyporiensis*, 187 *A. maculatus*, and 176 *A. hyrcanus*, the corresponding percentages were 3·63 and 3·21 for the first two species, while dissection of the others was negative. The explanation of this striking discrepancy would seem to be "animal deviation." At Wo-Li-Hop, where there are many buffaloes, oxen and pigs, the cowhouse, though sometimes separate, is often divided from the dwelling merely by a wall, while the pigsties are usually solidly built and well shut in. Animals at Shing-Mun, on the other hand, apart from dogs and goats, are practically non-existent. By way of control, precipitin tests (results given in a table) were made of the stomach-contents of mosquitoes caught at the two villages mentioned, and of others taken at Shouson-Hill in Hong Kong Island, where livestock consists chiefly of pigs kept in sties of a type unlikely to shelter anophelines. At Shing-Mun, where there are no cattle or pigs, 89 per cent. of mosquitoes of the four species mentioned above were gorged with human blood; at Wo-Li-Hop, on the other hand, out of 92 Anopheles caught for the most part in cowhouses, only 7 contained human blood, and even 23 out of 26 specimens of the notorious *A. minimus* proved to have been feeding on buffaloes.

In the opinion of the author, these and other results of what is admittedly a preliminary investigation "demonstrate the interest of the study of zoophily and of prophylaxis by means of zoophily in the Far East, and the possible importance of the correct housing of livestock as affecting the incidence of local endemic malaria."

E. E. A.

TOUMANOFF (C.). Quelques faits sur les habitudes trophiques des anophélines d'Extrême-Orient. [**Notes on the Trophic Habits of the Anophelines of the Far East.**]—*Bull. Soc. Path. Exot.* 1934. Dec. 12. Vol. 27. No. 10. pp. 932–936.

As is shown in a table, all oriental anophelines may attack animals, and precipitin results hitherto obtained serve to stress the importance

of the study of zoophily in the Far East. In the case of *Anopheles minimus* and *A. jeyporiensis*, chief malarial vectors in Indo-China and Hong Kong, buffaloes rather than cattle seem, on occasion, to replace man as hosts, and may perform a similar office for other paucidentate species. On the other hand, multidentate species, adapted to feeding upon livestock and of little or no account as malaria-carriers, have been found gorged with bovine blood where cattle alone were present. Where cattle but no buffaloes are kept *A. minimus* is definitely androphile, whereas *A. vagus*, governed perhaps, as are also probably other zoophile species, by an imperious tropism, battens especially on ox-blood.

The proportion of female mosquitoes of innocuous, non-malaria-carrying species found gorged with human blood inside dwellings is relatively small: thus, out of a total of 334 precipitin tests of the stomach contents of *A. hyrcanus* var. *sinensis*, *A. tessellatus*, *A. subpictus*, *A. barbirostris* and *A. vagus*, only 20 (5·9 per cent.) showed human blood. In the case of *A. vagus*, out of 261 tests on specimens caught in dwellings, only 9 reactions were positive with anti-human serum, and the percentage of animal blood in this species is sometimes 100.

In Cochin-China, contrary to what happens in Europe in the case of *A. maculipennis*, the absence of perfect stalling for cattle does not hinder completely the deviating effect of livestock upon the innocuous anophelines, which frequently use dwellings merely as retreats after feeding. Thus there is often an absence of correlation between the trophic habits of anophelines in Cochin-China and their ascertained presence in habitations. It is especially where livestock is absent or scarce that the innocuous Anopheles in houses contain human blood; in such places, should they have access to gamete-carriers, they may become dangerous.

A postscript by Roubaud emphasizes the theoretical and practical interest of Toumanoff's observations on deviation by the buffalo of paucidentate, typically androphile anophelines in the Far East.

E. E. A.

Toumanoff (C.) & Hu (S.). Premières données sur la zoophilie de *A. hyrcanus* var. *sinensis* en Chine (région de Shanghai). [**Zoophily of** *Anopheles hyrcanus* **var.** *sinensis* **in the Shanghai Region.**]—*Bull. Soc. Path. Exot.* 1934. Oct. 10. Vol. 27. No. 8. pp. 741–745.

Although several times found infected in nature (on one occasion in Sumatra 12 per cent. out of 3,638 specimens dissected were positive), *A. hyrcanus* var. *sinensis* as a vector of malaria is considered to be practically negligible. This mosquito, which has a well developed maxillary armature, feeds freely on animal blood, and as a rule becomes naturally infected only in isolated cases. At the same time, in certain parts of China, especially the regions of Shanghai and Nanking, no other anopheline is known to occur, so that *A. hyrcanus* var. *sinensis* is the only possible carrier of the local malaria. Using the precipitin test on material obtained from a small village some 10 miles from Shanghai, where the mosquito in question is very abundant in summer, both in dwellings and in cattle-sheds, while the incidence of malaria in the district is relatively slight, 295 out of 300 reactions were positive

for buffalo blood, while 4 more showed mixed buffalo and human blood. Thirty-five additional specimens were uniformly positive for buffalo blood. Since *A. hyrcanus* var. *sinensis* can readily be infected experimentally, the importance of zoophily as a safeguard to human communities in China is obvious. In Hong Kong, where cattle are nearly absent, the same species of mosquito is almost invariably gorged with human blood. *E. E. A.*

TOUMANOFF (C.). Caractéristique des représentants du "Rossii-Ludlowi" groupe de l'Indochine. Première note: *A. subpictus* Grassi. [**Characters of the Indo-Chinese Representatives of the "*Rossii-Ludlowi* Group." I.** *Anopheles subpictus.*]—*Bull. Soc. Méd.-Chirurg. Indochine.* 1934. Aug.–Sept. Vol. 12. No. 7. pp. 657–673. With 10 figs.

Much of this paper is concerned with a detailed comparison, in both the larval and the adult stages, of the Tongkingese form of *A. subpictus* (syn. *A. rossii*) with *A. subpictus* var. *indefinitus*, as found by KING in the Philippine Is. (see this *Bulletin*, Vol. 29, p. 479), and with the typical form as described by GRASSI. Notes are also given on the diagnostic characters of *A. subpictus* as it exists in Cochin-China, and on those of *A. vagus* in Tongking. Though in both Southern and Northern Indo-China *A. subpictus* appears to belong to the var. *indefinitus*, in Cochin-China it is to some extent intermediate between the variety and the typical form. *A. subpictus* in Tongking is best distinguished from *A. vagus* by the amount of black on the palpi in the female, and in the male by the length of the filament of the phallosome.

To what extent, if any, *A. subpictus* is a malaria-carrier, whether in Tongking or in Cochin-China, it is as yet difficult to say. *E. E. A.*

TREILLARD (M.). Tableau synoptique pour la détermination rapide des anophèles d'Indochine. I. Adultes. [**A Synoptic Table for the Rapid Determination of the *Anopheles* of Indo-China. I. Adults.**]—*Bull. Soc. Path. Exot.* 1934. Oct. 10. Vol. 27. No. 8. pp. 751–753.

Although numerous keys for the determination of Far Eastern Anopheles already exist, it is claimed by the author that the dichotomic method is not without drawbacks, chief among which are final uncertainty and the impossibility of comparing the same characters in all species, and the different species one with another. Figures of whole insects, in black-and-white or in colour, are likewise open to objection, and are difficult to manipulate. Taught by experience, Treillard prefers a combination of synoptic table and diagram, by means of which reliable determinations may be arrived at with ease and rapidity. The table at the end of this short paper includes, besides other details, a schematic representation of leg- and palp-markings in twenty-one species of Anopheles found in Indo-China. *E. E. A.*

EVANS (A. M.). **Further Notes on African Anophelines, with a Description of a New Group of *Myzomyia*.**—*Ann. Trop. Med. & Parasit.* 1934. Dec. 20. Vol. 28. No. 4. pp. 549–570. With 11 figs. [13 refs.]

In this paper, which is purely systematic, notes are given on *Anopheles distinctus* and its allies, and the following new species and

varieties are described:—*A. distinctus* var. *ugandae*; *A. Myzomyia schwetzi* (Belgian Congo; French Sudan); *A. theileri* var. *septentrionalis* (Uganda; Anglo-Egyptian Sudan); *A.* (*Myzomyia*) *wilsoni* (Tanganyika Territory): and *A.* (*Myzomyia*) *lovettae* (Tanganyika Territory). The two latter species constitute the new group *Eomyzomyia*, which is likewise described. The author also furnishes a "Provisional Key for separation of the females of *A. distinctus* and the Anophelines resembling it"; discusses the systematic position of *A. rufipes*; and adds notes on certain morphological characters of *A. ardensis*, *A. machardyi*, and *A. natalensis* and its var. *multicinctus*.

E. E. A.

Buxton (P. A.). **Further Studies upon Chemical Factors affecting the Breeding of *Anopheles* in Trinidad.**—*Bull. Entom. Res.* 1934. Dec. Vol. 25. Pt. 4. pp. 491–494.

Beattie, working in Trinidad, found, with regard to the hydrogen-ion concentration and CO_2 content, that "no definite correlation exists between the reaction of the water and the prevalence of *A. tarsimaculatus*" (see this *Bulletin*, Vol. 30, pp. 293–294). Nevertheless the prevalence of larvae of this mosquito in ponds appeared to vary inversely with the amount of ammonia nitrogen in the water, and there was reason to think that oviposition was possibly affected by this factor.

In the present paper Buxton endeavours "to make fuller use" of Beattie's original and hitherto only partly published data. As regards ammonia nitrogen, it is shown in a table that, although there is no very close correlation, "as the concentration of ammonia nitrogen rises, the number of larvae falls." When the numbers are examined statistically, it appears that "the effect of ammonia nitrogen only accounts for a little more than 12 per cent. of the variation in the number of larvae." In rice-field waters alone correlation is higher, but "only a little more than 18 per cent. of the variation in the number of larvae is attributable to the ammonia nitrogen." Since the figures of the latter are not uniformly high in all rice fields, it is probable that the ammonia results from sewage contamination rather than the actual cultivation of rice.

A second table, dealing with organic nitrogen, and the number of occasions when *A. tarsimaculatus* larvae were found in its presence, shows it to be a factor of less importance than that of ammonia nitrogen. While the conclusion that the latter "has a greater effect upon the numbers of larvae in Trinidad than any other of the factors which were studied" is possibly sound, the determination of the manner in which this factor acts is a matter for laboratory experiment rather than work in the field.

E. E. A.

Hill (Rolla B.). **Feeding Habits of Some Venezuelan Anopheles.**—*Amer. Jl. Trop. Med.* 1934. Sept. Vol. 14. No. 5. pp. 425–429.

Nine hundred Anopheles of various species, caught between July and October 1929, in three localities in the Lake Valencia region of Venezuela, where malaria is serious, were subjected to the precipitin test in order to determine the source of ingested blood. The results indicate that *A. albimanus* "feeds on human beings in large numbers,

and is probably the most dangerous species usually found in the Lake Valencia region" (out of 506 *A. albimanus* tested against human serum, 170, or 34 per cent., proved positive). *A. bachmanni*, although like *A. tarsimaculatus* definitely preferring animal blood, was positive to human antiserum in 14 cases out of 262 individuals tested, and is therefore "confirmed as a possible malaria carrier." *A. pseudopunctipennis*, on the other hand, though of importance in Argentina, would seem to be but a doubtful vector in the area mentioned above. *E. E. A.*

Russell (Paul F.) & Santiago (Domingo). **Flight Range of Anopheles in the Philippines. Second Experiment with Stained Mosquitoes.**—*Amer. Jl. Trop. Med.* 1934. Sept. Vol. 14. No. 5. pp. 407–424. With 4 figs. & 1 map.

In continuation of a previous experiment by the authors on similar lines (this *Bulletin*, Vol. 31, p. 720), 10,000 stained mosquitoes, chiefly of the *Anopheles funestus-minimus* subgroup, were released from one point. Out of 31,011 adult anophelines afterwards collected in all directions therefrom, up to a distance of 4 kilometres (2½ miles), 11 were stained. All but two of these were retaken to the south of the liberating place, during a strong north-east monsoon, and they included 8 examples of *A. minimus* var. *flavirostris*, "the chief malaria carrier of the Philippines," an engorged female of which was recaptured between 1¼ mile and 1 mile 660 yards down wind. It is concluded that *A. minimus* var. *flavirostris* (as also *A. subpictus* var. *indefinitus*) flies with, rather than against the wind, and in this way may travel at least 1¼ mile; also that "the northeast monsoon may have a pronounced effect in extending the flight range of the malaria-carrying anophelines of the Philippines." *E. E. A.*

Pires (Rubens Escobar). Contribuição para o estudo dos Anophelinos do grupo Nyssorhynchus (Diptera, Culicidae) do Estado de São Paulo. [**A Study of the Anophelines (Nyssorhynchus Group) in the State of São Paulo.**] [Thesis for Doctorate, Medical Faculty, São Paulo.]—89 pp. 1934. São Paulo: Imprensa Metodista. With 5 charts & 25 figs. [76 refs.]

This thesis, as its title indicates, gives a detailed description of the Nyssorhynchus group of Anophelines as found in São Paulo. The author has also provided keys to facilitate their determination and a series of 25 figures, 20 of them excellent reproductions of microphotographs, depicting special points in morphology. There is also appended an extensive bibliography. The work must have entailed much research and the result will be of service to entomologists and systematists. *H. H. S.*

Shannon (R. C.). **Malaria Studies in Greece. The Reaction of Anopheline Mosquitoes to Certain Microclimatic Factors.**—*Amer. Jl. Trop. Med.* 1935. Jan. Vol. 15. No. 1. pp. 67–81. With 1 fig.

The importance of the races of *A. maculipennis* in relation to malaria is different. Are these differences inherent, or have the races peculiar ecological needs which tend to cause some of them to seek shelter in houses more than others?

The author endeavours to study the reactions of certain Anopheles to microclimates by making observations in the Struma Valley in Macedonia. His method was to count the females by day in their resting-places, and most of his observations were made in a stable and in certain tunnels and shafts which were excavated for the purpose. With the aid of movable partitions he was able to some extent to control the climatic gradients in the tunnels.

The conclusion is reached that light is extremely important and that probably the light at or about dawn is an effective factor. But when light in a given part of the tunnel is constant, the number of females resting is affected by temperature, there being a preference for lower temperatures within the limits observed. A definite difference between species was noticed, the female *superpictus* tolerating a higher temperature than the female *maculipennis*.

The work is interesting and original, and represents an attempt to carry laboratory observations into the field. As there are so many variables only slightly controllable, it is obvious that the conclusions must be examined very critically. The reader will observe that the author groups together certain days and positions in which the microclimatic conditions appear to be similar, but we cannot discover how consistently the Anopheles behaved on separate days in each group. It would be interesting to see at least one set of figures put out at length and tested for homogeneity; indeed, one might say that, inasmuch as the problem consists of unravelling several factors without the use of strict experimental control, it is essentially statistical. No information is given as to the methods by which temperature and humidity were measured. It would surely be of value to install recording instruments, or at least to measure maximum and minimum temperature. We also lack information about the photometry, a difficult but important subject. *P. A. Buxton.*

i. Covell (G.). **Anti-Mosquito Measures with Special Reference to India.**—*Health Bull. No. 11. Malaria Bureau No. 3.* pp. ii+61. 3rd Edition. 1934. Delhi. Manager of Publications. [As.12 or 1s. 3d.]

ii. Sinton (J. A.). **Instructions for Collecting and Forwarding Mosquitoes.**—*Health Bull. No. 13. Malaria Bureau No. 5.* pp. iii+ii+70. With 23 figs. on 2 plates. Revised and Enlarged. Second Edition. 1934. Delhi: Manager of Publications. [As.12 or 1s. 3d.]

i. Although, as indicated in the title, Indian conditions have been specially considered, this extremely useful and valuable pamphlet is really an epitome of the experience gained by many workers in various parts of the world. Originally published in 1927, the booklet in its present edition has been to a considerable extent re-written, and several alterations of practical value have been made. The subject-matter is divided into three parts, respectively entitled :—" Protection against Bites of Mosquitoes" ; " Measures directed against Adult Mosquitoes" ; and " Measures directed against Larvae of Mosquitoes." It is scarcely necessary to say that, under the latter heading, the various methods of using Paris green, among other chemical larvicides, as a substitute for oil, receive appropriate attention. As regards the amount of oil to be used—a practical question often asked—it is considered that, although to some extent dependent upon circumstances, usually " half an ounce

of oil per square yard, or 15 gallons per acre, is an ample estimate." The advantage of adding a small percentage of vegetable (preferably castor) oil or cresol to increase spreading is duly noted.

A series of short appendices and a concise index conclude a work which should be in the hands of every sanitarian in the tropics.

ii. It is stated in the Preface to this new edition that it is " mainly a compilation of those methods which have been found by the workers of the Central Malaria Bureau and the Malaria Survey of India to be most suitable for the local conditions of this sub-continent." Since, as is now generally recognized, accurate determination of species, which presupposes antecedent good work on the part of the collector, is a primary necessity in any well-planned anti-mosquito campaign, the present treatise, which might be described as " The Intelligent Layman's Guide to Mosquito Collecting," is not the least important among the valuable Bulletins originally issued by the Central Malaria Bureau.

As in the case of the previous number, the precepts enjoined may be studied and followed with profit in any part of the world. *E. E. A.*

MATTHES (H. C.). **A Study of the Seasonal Distribution of Anopheles in Houston, Texas.**—*Amer. Jl. Hyg.* 1935. Jan. Vol. 21. No. 1. pp. 233–248. With 2 graphs.

Apart from brief notes on *A. crucians*, *A. punctipennis* and *A. pseudopunctipennis*, which occur chiefly during the colder months, this paper is concerned solely with *A. quadrimaculatus*, the common and important anopheline in Houston. In the southern section of the city the principal breeding-place is a spring-fed stream or bayou, but rice-fields 15 miles distant also produce adults in enormous numbers. Near the bayou, rainy periods, which cause the water to rise above the aquatic vegetation and thus expose the larvae to the attacks of top-minnows, produce most fluctuations in the abundance of *A. quadrimaculatus*, but the rice-fields area is not affected in the same way. On the other hand winter breeding, though suspended during cold spells, continues when the thermometer rises, and there is no indication that a definite number of broods is produced during the year. A fall of temperature below 20°C. causes rapid decrease in the number of adults, but, in the presence of appropriate breeding-places, the winged mosquito population definitely increases again at about 22° or 23°C.

E. E. A.

ROUBAUD (E.). Un type racial nouveau de l'*Anopheles maculipennis*. [**A New Race of** *Anopheles maculipennis*.]—*Bull. Soc. Path. Exot.* 1934. Oct. 10. Vol. 27. No. 8. pp. 737–740. With 2 figs. on 1 plate.

A previous paper by the author, with COLAS-BELCOUR and GASCHEN [see this *Bulletin*, Vol. 30, p. 305], referred to an experiment in crossing stenogamous males of *A. maculipennis* of Norman stock with large, eurygamous Dutch females. The Norman insects, originally found in the vicinity of Caen, and since maintained and studied in the laboratory for several years, are now considered to represent yet another race or variety of *A. maculipennis*, which is accordingly characterized in the present contribution as var. *fallax*.

The eggs of this new race, which are dark, dappled, and have broad floats, are of the *messeae* type. In details of egg-structure, although not in certain larval characters nor in the stenogamy of the zoophile, multidentate adults, var. *fallax* likewise approaches HACKETT'S var. *melanoon*, the validity of which, however, cannot yet be regarded as established. The larvae of the Norman race show affinity with those of the *typicus-messeae* group in certain morphological details, although there are discrepancies in others. Further approximation to the *typicus-messeae* group is seen in the number and shape of the harpagonal spines in the males.

Similar affinities are displayed on the biological side, var. *fallax* being homodynamous and ready to breed at all seasons. The great difference is in its stenogamy, as a result of which it breeds readily in a cage one-twentieth of a cubic metre in size; in this respect alone it agrees with var. *atroparvus*. On a biological basis, the position of the subject of this paper among the races of *A. maculipennis* whose characteristics are definitely known may be shown as follows :—

*Homodynamous	eurygamous :	*labranchiae*.
		typicus-messeae.
	stenogamous :	*fallax*.
Heterodynamous :	stenogamous :	*atroparvus*.

E. E. A.

BEKLEMISCHEV (W.). Ueber einige Gesetzmässigkeiten in der Larvenoekologie von *Anopheles maculipennis* : das Optimum der Pflanzenabundanz. [**The Larval Oekology of** *A. maculipennis* : **Influence of Vegetation.**]—*Med. Parasit. & Parasitic Dis.* Moscow. 1934. Vol. 3. No. 5. [In Russian pp. 361–376. With 4 figs. [26 refs.] German summary pp. 376–377.]

Deals in detail with the relations of *A. maculipennis* larvae to floating and submerged vegetation, discussing the favourable and unfavourable factors. *A. G. B.*

CORRADETTI (Augusto). Richerche sugli incroci tra le varietà di *Anopheles maculipennis*. [**Crosses between the Races of** *A. maculipennis*.]—*Riv. di Malariologia*. Sez. I. 1934. Vol. 13. No. 6. pp. 707–720. With 4 figs on 1 plate. English summary.

" The results of crosses between the Italian *A. mac. atroparvus* and *A. mac. typicus*, *A. mac. messeae*, *A. mac. elutus* are first described. The males of the Italian *atroparvus* mate in confinement with the females of the other *maculipennis* races, but the reverse does not occur; furthermore, the crosses of the first hybrid generation are not fertile, owing to the high incidence of the atrophy of the testicles and ovaries. Then it appears that the behaviour of the Italian *atroparvus* in these crosses is the same as that of the Dutch *atroparvus*. From other researches, carried out on the crosses and re-crosses between *A. mac. labranchiae* and *A. mac. atroparvus*, it results that the eggs deposited by the F_1 generation show intermediate

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*Although what the late Lt.-Col. ALCOCK once described as " the opulent terminology apparently inseparable from the subject " must by this time be fairly familiar to readers of papers on races of *A. maculipennis*, the combined effect of four of these formidable-looking terms in close order is somewhat overwhelming. A glossary is accordingly appended :—

Homodynamous, not subject to complete hibernation.
Heterodynamous, subject to complete hibernation.
Eurygamous, not mating in a confined space, but needing to make a nuptial flight as a preliminary to copulation.
Stenogamous, breeding freely in cages of very limited dimensions. *E. E. A.*

characters between the *labranchiae* and *atroparvus* eggs. According to Mendel law, the distribution of these characters are 75 per cent. for the dominant (*A. mac. atroparvus*) and 25 per cent. for the recessive (*A. mac. labranchiae*).

" If F_1 is eurygame or stenogame, has not been established; inter-breeding (males and females of the F_1) fertile eggs have not been obtained.

" This negative result is difficult to explain; the males show normal testicles only in 10 per cent. of the cases.

" In the second generation obtained through the re-cross of the hybrid female with the *atroparvus* male, the stenogame character is dominant. For this reason inter-breeding is possible. The eggs deposited are fertile; in 70 per cent. of the cases the males show normal testicles.

" The results of Roubaud and the Dutch authors on the possibility of crosses between the *atroparvus* females and *labranchiae* males are confirmed."

Raymond-Hamet. Démonstration expérimentale, sur l'animal entier, de l'action vasodilatrice de la quinine. [**The Vasodilator Action of Quinine Demonstrated in the Living Animal.**]—*C. R. Soc. Biol.* 1935. Vol. 118. No. 3. pp. 231–233. With 1 fig. [18 refs.]

Quinine was injected into the deep femoral artery of a vagotomized dog. The blood pressure and the flow of blood were measured. The blood pressure fell continuously with the escape of blood, but nevertheless the flow became twice as fast after the injection of quinine, owing to vaso-dilatation. *W. F.*

Bernardbeig & Caujolle (F.). Sur l'élimination de la quinine par la bile. [**Elimination of Quinine by the Bile.**]—*Bull. Acad. Méd.* 1935. Jan. 29. 99th Year. 3rd Ser. Vol. 113. No. 4. pp. 147–151. With 1 fig. [30 refs.]

A woman of 58 who had had a cholecystostomy with a resulting biliary fistula received intravenously a dose of quinine of 0·0034 gm. per kilo. Quinine appeared in the bile 15 minutes after the beginning of the administration. The author points to the importance of this observation owing to the large surface offered by the intestine for reabsorption. Details of technique are given. *A. G. B.*

Stoker (W. J.). Over de malariagevaarlijkheid van *A. leucosphyrus*. [**Malaria Infection Rate of** *A. leucosphyrus* **(Borneo).**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1934. Oct. 9. Vol. 74. No. 21. pp. 1342–1344. English summary (2 lines).

In the village of Sarang-Tioeng (Borneo) of 110 *A. leucosphyrus* examined 7 were found infected with malarial parasites (6·4 per cent.). *A. G. B.*

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de Buck (A.) & Swellengrebel (N. H.). Further Observations on the Pattern of the Upper Surface of the Ova in the Dutch Varieties of *A. maculipennis*.—Reprinted from *Proc. Acad. Sci. Amst.* 1934. Vol. 37. No. 8. pp. 578–579. With 7 figs. on 1 plate.

de Buen (Eliseo). Estudios sobre la biologia del *Anopheles maculipennis* Meig. Indice maxilar y longitudes de ala, abdomen y tórax.—*Medicina Países Cálidos.* Madrid. 1935. Feb. Vol. 8. No. 2. pp. 73–84. With 9 figs.

Courel Fernández (Miguel). Memoria de la campaña anti-palúdica de 1932 en Castrelo de Miño (Orense).—*Rev. San. e Hig. Pública.* 1934. Nov. Vol. 9. No. 11. pp. 460–470. With 5 graphs & 1 fig.

Ferreira (Barreto Gonçalves). Malaria no Recife.—*Folha Med.* 1934. Oct. 5. Vol. 15. No. 28. pp. 329–331.

GALLIARD (H.) & SAUTET (J.). Quelques caractères morphologiques d'*Anopheles elutus* de Corse.—*Ann. Parasit. Humaine et Comparée.* 1935. Jan. 1. Vol. 13. No. 1. pp. 1–4. With 2 figs.

GIOVANNOLA (A.). Dopo 300 anni da una grande rivoluzione nel campo della medicina. La scoperta della china nella leggenda e nella storia.—*Riv. di Malariolgia.* Sez. II. 1934. Vol. 13. No. 3 bis. pp. 169–174. With 2 figs. [10 refs.]

GUY (R.). Note sur l'endémie palustre à Luang-Prabang (Haut-Laos).—*Bull. Soc. Méd.-Chirurg. Indochine.* 1934. Oct. Vol. 12. No. 8. pp. 766–791. With 4 charts & 1 folding plan.

——. Quelques index d'endemicité palustre dans la Haute-Région laotienne (Luang-Prabang).—*Bull. Soc. Méd.-Chirurg. Indochine.* 1934. Oct. Vol. 12. No. 8. pp. 792–806. With 1 map.

HAMEL (J.) & CHAVAROT (M.). Contrôle de la guérison des impaludés thérapeutiques par la réaction de Henry.—*C. R. Soc. Biol.* 1935. Vol. 118. No. 1. pp. 93–94.

HENRY (A. F. X.). Réactifs mélaniques et mélanoferriques solubles et en suspension.—*C. R. Soc. Biol.* 1935. Vol. 118. No. 6. pp. 501–504.

JANA (A. P.). Treatment of Enlarged Spleens with Injections of Milk.—*Indian Med. Gaz.* 1934. Dec. Vol. 69. No. 12. pp. 687–688.

KIRK (Robert). A Case of Intra-Uterine Malarial Infection.—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1935. Jan. 25. Vol. 28. No. 4. pp. 421–424. With 2 charts.

LEGENDRE (F.). Note sur une tournée de prospection antipalustre à Ambatondrazaka et dans la région du lac Alaotra.—*Bull. Soc. Path. Exot.* 1934. Dec. 12. Vol. 27. No. 10. pp. 957–960.

MARZINOWSKY (E.). Indice terapeutico en la infeccion paludica.—*Medicina Paises Cálidos.* Madrid. 1935. Feb. Vol. 8. No. 2. pp. 104–105.

MOREAU (P.). Notes sur un voyage d'études malariologiques dans l'Océan Indien. (Java.—Iles Mascareigues.—Afrique du Sud.)—*Bull. Soc. Med.-Chirurg. Indochine.* 1934. Aug.–Sept. Vol. 12. No. 7. pp. 674–703. With 6 figs. on 3 plates & 1 chart.

NÄGELSBACH (E.). Malaria tertiana unter dem Bild eines Magendarmkatarrhes. —*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. Mar. Vol. 39. No. 3. pp. 126–127.

PAOLO (Romby). Au sujet du pigment des parasites du paludisme.—*Boll. Sezione Ital., Soc. Internaz. di Microbiologia.* Milan. 1934. Nov. Vol. 6. No. 11. pp. 451–456.

SCHWETZ (J.). Quelques considérations et réflexions sur l'immunité malarienne. —*Riv. di Malariologia.* Sez. I. 1934. Vol. 13. No. 5. pp. 669–678.

VAN SLYPE (W.). Sur la valeur curative et prophylactique de l'atébrine injectable.—*Ann. Soc. Belge de Méd. Trop.* 1934. Sept. 30. Vol. 14. No. 3. pp. 379–383.

TEGONI (G.) in collaboration with B. Williams AURELI. Indice bibliografico della malaria.—Supplement to *Riv. di Malariologia.* 1932. Vol. 7. 130 pp.

UHLENHUTH (Paul). I. Neuere Forschungsergebnisse bei der Heilung und Bekämpfung der Malaria.—Reprinted from *Ztschr. f. Ärtzliche Fortbildung.* 1934. No. 14. pp. 393–396.

WYNNE (A. M.). Some Observations on the Newer Methods of Malaria Control. —*New Orleans Med. & Surg. Jl.* 1935. Jan. Vol. 87. No. 7. pp. 435–439.

YOFÉ (Hillel). Contribution à l'étude du traitement moderne du paludisme.—*Rev. Méd. et Hyg. Trop.* 1934. Sept.–Oct. Vol. 26. No. 5. pp. 225–231 [18 refs.]

PLAGUE.

Eskey (C. R.). **Epidemiological Study of Plague in the Hawaiian Islands.**—*Public Health Bull. No. 213.* Wash. 1934. Oct. 70 pp. With 6 figs. (2 maps).

Public Health Reports. 1935. Feb. 22. Vol. 50. No. 8. pp. 255–257.—**Epidemiological Study of Plague in the Hawaiian Islands.**

In view of the tendency of plague to spread by sea-going vessels to distant ports the Hawaiian Islands, lying as they do on the trans-Pacific trade routes between North America and the Orient and Australia, have a special epidemiological importance. They are " The cross roads of the Pacific." A very complete study of plague in these islands is presented in this monograph : it contains many points of general interest in addition to those for official record.

The first case of plague occurred in Honolulu, December 12, 1899 and " the source could have been Hongkong or it could have been Japan." There followed on the islands 17 cases in December 1899, 35 in January 1900, 10 in February and 9 in March and so the epidemic was launched. Human cases have occurred every year since although, at the present time, they are very few in number. Two important epidemiological types of plague have been differentiated, the one of short duration where practically all cases occurred within towns or villages, the other long, persistent and occurring " on isolated rural premises " with a finding of infected rodents at great distances from buildings in fields and gulches. The two types are designated urban and rural respectively. A marked difference of the same order was found in the distribution of the two species of flea *Xenopsylla cheopis* and *X. hawaiiensis*. The latter was first detected on rats in 1932 and it has a similarity to the *X. astia* of Asia. Infestation of rats by fleas has a marked difference according as the rat is caught in or at a distance from buildings. Thus one table shows the *X. cheopis* index for female rats to be 3·57, 1·66, 0·5 and 0·26 respectively according as the host animal was caught inside building, under and within 50 ft. of building, 50 to 200 ft. and over 200 ft. from building. These indices may be contrasted with a series of similar figures for *X. hawaiiensis*, which were respectively 0·2, 0·35, 0·55, 0·87, 0·66, 0·86, 0·72 and 1·01 under the following conditions :— Inside building, under 25 to 100 ft. from building, 300 to 500 ft., 500 to 1,000 ft., and over 1,000 ft. from building. Therefore in the Hawaiian Islands *X. cheopis* infestation decreased with distance from buildings and *X. hawaiiensis* was more prevalent at a distance or on rats harbouring in fields and gulches.

Starvation survival of fleas is considered by many recent authors to be of great importance. The experiments here recorded showed that when *X. cheopis* were removed from wild rats none lived longer than 9 days while those collected from laboratory jars remained alive for 13 days. As regards the rôle of the fleas mentioned in the transmission of plague the author states that *X. cheopis* " were probably the infecting agents responsible for nearly all human cases " and that " epidemiological evidence indicates that *X. hawaiiensis* is the plague transmitting agent among field rats responsible for the endemic type of infection " in certain regions of the islands. There is a " native " rat as well as a native flea : it was described as *Rattus hawaiiensis* in 1917 and is closely related to the Malay rat, *R. concolor*.

Plague control measures are considered in the concluding pages of this monograph and are summarized as follows :—(1) " Rat proofing will eliminate the chief breeding places of *X. cheopis* as well as the rat population of buildings," but " rat proofing will not control endemic plague of field rats transmitted by *X. hawaiiensis*."

(2) " Trapping rats is a costly and ineffectual means of reducing the rat population especially of field rats."

(3) " Poisoned grains distributed in the form of paper packages . . . have proven to be a very safe method for using poison. . . . The attractiveness of grains may be enhanced by mixing them with coconut, bacon, or fresh fat, and other food stuffs. . . Poisons have to be employed constantly or the rat population soon returns to its normal level." As poisons white arsenic in ten per cent. mixtures was used in field work and thallium sulphate in 5 gm. packages of a mixture of 3 lbs. to 1,000 lbs. of grain " in and near buildings, where there was the greatest danger of accidents occurring." *W. F. Harvey.*

i. Savino (Enrique). Tres brotes pestosos en las provincias de Salta, Jujuy y San Luis. [**Three Outbreaks of Plague in Argentina.**]—*Rev. Inst. Bacteriológ.* Buenos Aires. 1934. Mar. Vol. 6. No. 2. No. 99–129. With 4 maps & 19 figs. English summary.

ii. ——. Un nuevo brote de peste en Recreo (prov. de Catamarca). [**A New Epidemic of Plague in Catamarca.**]—*Ibid.* July. No. 3. pp. 295–303. With 6 figs. English summary (7 lines).

iii. De la Barrera (J. M.) & Arzeno (M.). Brote de peste en la prov. de Córdoba. [**Outbreak of Plague in the Province of Cordoba.**]—*Ibid.* pp. 330–341. With 6 figs. & 1 map.

i. The first of these outbreaks of plague, in which the majority of cases were pneumonic, probably took its origin from a case of secondary plague pneumonia in a child and was preceded by a rat epizootic. In the second epidemic the site of the plague was at 2,000 metres above sea level and was only accessible by a mule track, thus illustrating how plague may reach very isolated places by little frequented routes. The third outbreak arose from a rat epizootic in a grain shed, affected only the human population in the neighbourhood, and was bubonic in type.

ii. This is the third epidemic of plague which has appeared in the village of Recreo in the Argentine since 1920. Nine human cases of bubonic plague with 3 deaths occurred and there was the usual accompaniment of an epizootic. No trace of any epizootic, however, was found among wild rodents.

iii. This is an account of a small epidemic in the Argentine province of Córdoba comprising 15 cases of bubonic plague with a mortality of 46·66 per cent. The origin of the epidemic is not at all clear. Rats were numerous in the territory but were not found either dead or sick, nor was there much evidence of contact of wild rodents with man.

W. F. H.

Uriarte (Leopoldo) with the co-operation of Blanca Calcagno, Marcus Riesel & Benjamin Anchezar. Pulgas y peste. [**Fleas and Plague.**]—*Rev. Inst. Bacteriológ.* Buenos Aires. 1934. Mar. Vol. 6. No. 2. pp. 57–98. With 1 fig. & 12 plates (2 coloured). [Refs. in footnotes.] English summary.

Previous work on the infestation of rats by different species of fleas had shown that in Buenos Aires the percentage of *X. cheopis* was as

high as 95 per cent. More recent investigation (1927–1932) has brought down this high relative proportion by the inclusion of other species. A total of 30,389 rats was examined, of which only 722 (2·37 per cent.) carried fleas. The total number of fleas was 1,439 and the index (0·04 per cent.) was very low. Relative proportions of the different species, in percentages, were *X. cheopis* 61·25, *Ceratophyllus fasciatus* 31·54, *Leptopsylla segnis* 5·76, *Ctenocephalus felis* 0·66, *Ceratophyllus londiniensis* 0·26, *Pulex irritans* 0·2, *Craneopsylla wolffhuegeli* 0·2. The last of these, which is ordinarily a parasite of a purely field rodent, was found on the rat for the first time. *W. F. H.*

Peryassú (Antonio). Peste. Determinação dos fócos latentes de peste, pelo exame systematico de ratos, para verificação de portadores da "Pasteurella pestis." [**Systematic Examination of Rats to determine Plague Foci.**]—*Brasil-Medico.* 1934. Mar. 17. Vol. 48. No. 11. pp. 190–191.

Examination of rats in a plague area has shown that a certain number may be found infected as carriers, although presenting none of the usual gross characters of the disease. The finding of these, if the examinations are kept up in interepidemic periods, precedes the discovery of mild cases at the beginning of an epidemic. The recommendation of the author to examine all rats caught and to test their infectivity by inoculation has been carried out in Rio de Janeiro. During the past three years 45,151, 63,559 and 75,348 rats, have been examined and their livers and spleens inoculated into guineapigs. No rats were found infective by direct examination; of the guineapigs 875 died but none was found infected. Rio has been free from plague since the beginning of 1930, and no infected rats have been seen since July 26th, 1929.

In addition 1,492 rats from ships anchored in the harbour of Guanabara or in transit have been similarly examined, but none have been recorded as positive. The author concludes "Dealing with so large a number by direct examination and inoculation, we can guarantee the eradication of plague from our Capital Federal. This is an example of a sanitary measure which ought to be copied in the whole of Brazil." *H. H. S.*

Long (John D.) & Mostajo (Benjamin). Experiencias con pulgas como portadoras de peste bubónica. [**Fleas and Bubonic Plague.**]—*Bol. Oficina Sanitaria Panamericana.* 1934. Nov. Vol. 13. No. 11. pp. 1016–1024. With 1 map.

The authors state that bubonic plague was first introduced into the western coast of South America in April 1903, by way of the ports of Callao and Pisco, Peru. Since then there have been some 21,000 cases, or an average of 700 annually. It is significant that in the 37 Peruvian ports where plague has appeared, it has done so in places widely separated rather than in adjacent ports, in the wake of coastal vessels.

The infection appears to be conveyed in vessels with cargoes of jute and such like. They quote the case of s.s. *Solafric* from Calcutta in February with a cargo of 2,715 tons of bags, jute sacks and cordage; 2,911 bales were consigned to Peruvian ports, which she reached at the end of April 1933. They trace its calling places in Peru

and the appearance thereupon of plague rats and human cases. A map shows the sequence clearly. Fleas found in the bales of jute were identified and the commonest were *X. cheopis*, others being *Leptopsylla musculi* and *Hectopsylla* in small numbers.

In their summary the authors conclude that cases of bubonic plague arising unexpectedly and out of season in Peru nearly always occur on sugar or cotton estates where a large amount of jute or other sacking is used and are due to " infection imported by fleas carried in cargos of jute," and that the recent appearance of the disease in the Canete valley and in Callao, Chimbote and Eten was due to such importation, while the same explanation would account for certain cases in Lima and its neighbourhood, although it has not been possible to determine accurately the spread of infection there. *H. H. S.*

Léger (J. P.). Une saison de peste en brousse malgache. [**A Season of Plague in the Bush in Madagascar.**]—*Ann de Méd. et de Pharm. Colon.* 1934. July–Aug.–Sept. Vol. 32. No. 3. pp. 293–308.

This communication tells of the occurrence of plague which, owing to the burial customs and the habits of a primitive people, was able to reach considerable proportions before it was recognized. It was a more than usually severe epidemic and followed the usual rodent epizootic in rats of the *rattus* and *alexandrinus* type. A forest type of rodent, *Brachytarsomys albicauda*, not yet described as subject to plague was one of those affected. Plague appears regularly in these bush regions in the hot season and disappears with the coming of the rains.

W. F. H.

Roubaud (E.) & Mezger (J.). Présence à Madagascar de *Dinopsyllus lypusus* J. et R. puce pestigène des rongeurs de l'Afrique du Sud. [**Presence in Madagascar of** *D. lypusus*, **a Plague-carrying Flea of S. African Rodents.**]—*Bull. Soc. Path. Exot.* 1934. Oct. 10. Vol. 27. No. 8. pp. 740–741.

The specimens which proved to be this flea were collected 200 km. from Antananarivo. Members of this genus have hitherto been met with in Uganda, Kenya and S. Africa, not in Madagascar. *D. lypusus* infests a number of rodents [see this *Bulletin*, Vol. 30. p. 567], bites man, and experimentally transmits plague to gerbilles. Among 2,000 fleas collected in Madagascar only 15 were of this species. It is not known whether it transmits plague there. *A. G. B.*

Armstrong. Les événements épidémiologiques survenus du 1er juillet au 20 novembre 1934 [en A.O.F.]. [**Epidemiological Events in French West Africa from July 1st to November 20th 1934.**]—*Bull. Soc. Path. Exot.* 1934. Dec. 12. Vol. 27. No. 10. pp. 952–953.

The account given of epidemiological events relates to plague, typhoid fever, diphtheria, dysentery, measles, leprosy, relapsing fever and trypanosomiasis. At Dakar the year was notable for the great frequency of pneumonic plague, 161 cases altogether, of which 61 were primary. It is interesting to note that prediction of the severity of the coming plague season was made at the beginning of the year and that this proved to be true. This prediction was based upon the density of

the murine invasion and the exceptional abundance of fleas. No correlation was found between meteorological features and plague frequency. *W. F. H.*

GILMOUR (C. C. B.). **Bubonic Plague, Rats and Fleas in Singapore.**—*Malayan Med. Jl.* 1934. Dec. Vol. 9. No. 4. pp. 177–181. With 3 figs.

Plague has never become a menace in Singapore: the factors of transmission there are discussed.

It is now thirty years since plague made its first appearance in Singapore and that should be a sufficient length of time to take stock of the facts and "perhaps draw conclusions." The facts in this article are taken from the Annual Reports of the Municipal Officer of Health of Singapore and from observations in the laboratory. There have been 712 deaths representing the very high mortality of 93 per cent. and these were distributed as follows:—Chinese 605, Indians 120, Malays 24, other nationalities 15. And yet, in spite of the high mortality plague has had no significant effect on the general death rate of the town. Climatic conditions deserve the name of "equable" in Singapore, for the mean temperature hardly varies at all throughout the year, humidity shows little variation and there are no seasons. Plague cases have occurred in every month of the year for thirty years, but there is a close correlation between human plague and wet weather. The predominant rat in the town is *M. decumanus* and the predominant flea *X. cheopis*, but more fleas are found on *M. rattus* than on *M. decumanus*. The flea index is low and during late years especially so. Several graphs and tables are given, the first of these being that of plague cases from 1901 to 1929. A low plague rate is manifest for at least the last three of these years. A suggestion is made by the author that ants may help to keep down the flea population. *W. F. H.*

GRIKUROW (W.). Zur Frage der Aufbewahrung des Pestvirus im endemischen Herd während der interepizootischen Periode. [**On the Preservation of the Plague Virus in an Endemic Area during the Inter-Epizootic Period.**]—*Rev. Microbiol., Epidémiol. et Parasit.* 1934. Vol. 13. No. 3. [In Russian pp. 207–211. German summary p. 211.]

With a view to establishing the causes of endemicity in a plague area, observations were conducted on the susliks [*Citellus pygmaeus*] inhabiting twelve areas of 9 hectares each in a district of Northern Caucasus. The rodents which survived the summer epizootic (1932) were left unmolested till next spring (1933), when 450 of them were caught and isolated for further observations. Most of the animals perished in captivity without showing any symptoms (clinical and bacteriological) of plague infection. However, in one individual *Past. pestis* was isolated in culture, which produced a typical fatal infection in a control animal. It is concluded that during the inter-epizootic period the infection is latent in the body of the susliks and various factors, such as exhaustion and other conditions, provoke a generalized infection which ultimately gives rise to a plague epidemic in the suslik population. *C. A. Hoare.*

Dobradin (P. M.) & Skorodumov (A.) [Edited by]. **[Collected Works of the Anti-Plague Organization of the Eastern Siberian Region for 1929–1931.]** [*Trans. East Siberian Reg. Inst. of Microbiol. & Epidemiol.* Irkutsk. 1933. Vol. 1. 120 pp. With 10 figs. & 3 charts. (In Russian.)]

The anti-plague organization of Eastern Siberia is concerned with co-ordinating the work of the various laboratories and stations scattered throughout the region. The present volume comprises reports of the activities of these institutions (between 1929 and 1931) and a number of special articles among which the following may be noted.

V. V. Shunaev (p. 42) records the results of an experimental infection of a hibernating tarabagan (*Arctomys bobac*) with *Past. pestis*, resulting in the formation of a cutaneous plague ulcer which persisted until the death of the animal two months later. The chronic course of the infection serves to elucidate the origin of the early spring outbreaks among rodents and human beings. The same author (p. 43) failed to infect a wolf *per os*, while hares were found to be susceptible. V. L. Petrovsky (p. 45) describes a case of spontaneous plague in a polecat (*Putorius eversmanni*), probably acquired by feeding on infected rodents. Shunaev (p. 50) tested the viability of the plague bacillus under winter conditions by placing drops of a two-days' culture of *Past. pestis* on pieces of cloth and exposing them in sterile Petri dishes to temperatures varying between −10° to −47°C. Cultures taken from this material 45 days later remained infective to guineapigs. A. M. Skorodumov (p. 51) tested the effect of freezing and thawing upon the virulence of the plague bacillus in cultures and in animal corpses, by subjecting them to the influence of the external temperature during the winter months. The bacilli retained their virulence for periods from 3 to 5½ months.

Petrovsky (p. 55) determined the localization of *Past. pestis* in the organs of experimentally infected tarabagans. When inoculated subcutaneously the bacilli appear in the lymph glands from the fourth day; when introduced intraperitoneally they appear in the spleen, liver, kidneys and testicles on the third day, whereas they could not be isolated from the blood until the sixth day; after inoculation through the abraded skin of the abdomen the appearance of the bacilli in the parenchymatous tissues is delayed till the eighth day. P. N. Bekreneva (p. 60) devotes a paper to the distribution of the plague bacillus in the body of a vole, *Microtus brandti*, after subcutaneous inoculation. The bacilli first penetrate into the nearest lymph gland whence they find their way into the blood and are carried into the spleen, lungs, intestine and kidneys. The occurrence of these micro-organisms in the urinary bladder, in the faeces and in the urine indicate the method by which they are discharged into and contaminate the external medium. A. M. Skorodumov and L. A. Mitchurina (p. 72) describe the effect of pyoctanin and rivanol upon plague cultures and experimentally infected guineapigs. Both drugs have a bactericidal action *in vitro* in dilutions of 0·01 and 0·02 per cent. However, their therapeutic and prophylactic effect in animals is negligible. Skorodumov (p. 79) describes a method for the differential diagnosis of *Past. pestis* and *Past. pseudotuberculosis rodentium*. When grown on nutritive agar media containing 0·3 per cent. Congo red and various sugars or glycerine, the two bacilli produce colonies differing in colour

and appearance. I. G. Ioff and A. M. Skorodumov (p. 88) give a description and list of the fleas found on animals in the endemic plague area of Transbaikalia. *C. A. Hoare.*

Williams (A. W.). **Some Unusual Forms of Plague.**—*East African Med. Jl.* 1934. Oct. Vol. 11. No. 7. pp. 229–232.

In an area where bubonic plague is endemic and where, consequently, pneumonic or septicaemic plague can occasionally occur there is always the liability of admission of unsuspected cases to hospital. That is highly dangerous for fellow patients, when the case is one of pneumonia. "In any blood infection the clinical picture varies according to the system on which the brunt of the infection falls—hepatic, pulmonary, meningeal—a fact well illustrated by the records of these five cases." The five patients were admitted with symptoms resembling (1) toxic jaundice of yellow fever type, (2) primary meningitis, (3) pneumonia with delayed resolution and recovery, (4) in two cases, lobar pneumonia. The lesson to be drawn from such occurrences is that the sputum of all cases resembling pneumonia ought always to be examined for *P. pestis* whenever an outbreak of plague occurs or in an endemic area, as soon as the patient presents himself for admission. *W. F. H.*

Girard (G.). Technique simple et pratique de prélèvements pour identification du bacille pesteux chez l'homme. Son application au dépistage de la peste à Madagascar. [**Simple Technique for Diagnosis of Plague.**]—*C. R. Soc. Biol.* 1934. Vol. 117. No. 32. pp. 601–603.

A simple technique for diagnosis of plague with material sent from a distance has been tested by the author. In the case of a patient the bubo is repeatedly punctured with a syringe, which is well washed out after each puncture with sterile normal salt solution. In the case of a dead body the same procedure is gone through, but it is the lungs or liver which are punctured. A suspension is obtained from the washings and this is inoculated by friction on the shaved and scarified skin of the guineapig. Material obtained 3 to 10 hours after death in the animal experiments was capable of causing acute plague, up to a minimum of 6 days, when kept at a temperature of 16° to 26°C. If kept at 37°C. the infective period was reduced to 3 days. If the animal had been dead 48 hours (local temperature 21°C.) and putrefaction had set in, the suspensions were only virulent for 24 hours, the organs for 3 days. These animal experiments have been confirmed in actual practice with material sent to the laboratory from distant parts. *W. F. H.*

Kirschner (L.). Gal als voedingsbodem bij de diagnose der pest septichaemie. [**Bile Nutrient Medium in the Diagnosis of Plague.**] —*Geneesk. Tijdschr. v. Nederl.-Indië.* 1934. Aug. 28. Vol. 74. No. 18. pp. 1141–1159. With 1 chart. [31 refs.] [Summary appears also in *Bulletin of Hygiene.*]

Bile has now for a long time been used to obtain pure blood cultures of typhoid group bacilli, while the bile salts have also been employed in the further process of purification. The author has applied similar procedures to the cultivation of the plague bacillus from blood or pus and found them successful.

It was already known that a septicaemia exists in the first three days of bubonic plague and is also found one or two days before death. After the addition of blood to bile (1 in 2 up to 1 in 100), or as the case may be pus (1 in 10 up to 1 in 100), an inoculation of a very small number of plague bacilli (10 to 40 per cc.) gave a good growth. The bile may be sterilized either by filtration or by heat (20 minutes at 110°C.) and the addition even of one drop of blood to 5 cc. bile is sufficient to show up a light septicaemia. From this preliminary culture inoculations may be continued upon ordinary agar, Endo, or Drigalski agar. The original bile inhibits the growth of cocci and the components of the continuation media inhibit the growth of cocci and Proteus bacilli. By the use of this enrichment method the author was able with a single trial to demonstrate a bacteraemia in 212 out of 237 definite plague cases. *W. F. H.*

MADRAS. **Report of the Director of Public Health for 1933** [HESTERLOW (A. M. V.), Acting Director].—169 pp. 1934. Madras: Govt. Press. [pp. 42–45, paras. 76–79. **Plague Research ;** pp. 45–46, paras. 80–82. **Research on Bacteriophage.**]

Work of considerable importance is shortly described under the heading of plague research in the Cumbum Valley, *e.g.*, the infectivity of starved fleas; climatic conditions in rat burrows; value of bacteriophage.

Definite evidence of smouldering epizootics all the year round was found for some of the larger villages. This perpetuation is ascribed to the persistence of infection in rat fleas, even under conditions of deprivation of food for over four weeks. Wild rodents prevalent in the Cumbum Valley are moles of the species *Gunomys* Kok, gerbils, field mice, bush rats, bandicoots and house mice but although many of these have been proved to be very susceptible to plague they were not found to be naturally infected to any extent. Special stress has been placed on a research into the longevity of plague-infected rat-fleas under natural conditions in model houses. In the first of these experiments a positive transmission was obtained after continuous starvation for 63 days, while in the third experiment infected fleas transmitted their infection even after periods of starvation of 6, 14, 22 and 29 days. Seven instances were found in this experiment of resolving plague in the test-rats, and this suggests the possibility that the bacillus had lost virulence with starvation of the carrier flea. Another point of importance for possible carry-over plague conditions is to be found in the climate conditions in rat-burrows. A special thermograph was used for record and it was shown that although the outside temperature might vary from 86·5°F. to 63°F. the temperature within the burrows ranged only from 79°F. to 72°F., thus proving how little the temperature in these burrows was affected by external diurnal variation. Again it was demonstrated " that a fairly uniform high humidity is maintained in rat-burrows, while the outside atmosphere shows wide variations."

In summary of these facts it may be stated " that the rat-burrow provides optimum facilities for plague infection in fleas to tide over the unfavourable hot months." A further research was directed to the value of cyanogas fumigation of rat-burrows in the prevention of plague. The evidence afforded is strongly suggestive of value and especially in the case of Cumbum village itself " which has remarkably escaped

human plague. . . . Prompt fumigation . . . arrested the course of epizootic plague and thus prevented the outbreak of human plague."

Bacteriophage research in cholera has not yielded clear-cut results. The conclusions arrived at are:—" (1) The prophylactic administration of bacteriophage has not been shown to be effective in reducing the rate of attack. (2) The prophylactic administration of bacteriophage seems to lessen the mortality rate. (3) It has not been shown that bacteriophage is more useful than pro-diarrhoea mixture in the treatment of cholera." *W. F. H.*

GIRARD (G.) & ESTRADE (F.). Nouvelle observation de peste dans un élevage de lapins et de cobayes consécutive à une épizootie murine. [**Plague among Rabbits and Guineapigs of a Breeding Establishment following a Rat Epizootic.**]—*Bull. Soc. Path. Exot.* 1934. Dec. 12. Vol. 27. No. 10. pp. 962–963.

On the 8th June there were brought to the laboratory of the Pasteur Institute two rabbits, which had died in their hutch. Next day a guineapig from the same place was brought and this was the only survivor of 15 animals. It died within 24 hours. The autopsy, examination of liver and spleen smears, the inoculation of guineapigs, and the identity of the culture in the case of all three animals led to the conclusion that the infection was plague and not a pasteurellosis nor pseudo-tuberculosis. It was found that a dead rat had been discovered in one of the animal hutches on the 29th May, three more on the next day and seven on the 1st June. Then the guineapigs began to die and after that the rabbits. The dead rats discovered were 17 in all. It was not till the 7th June that the proprietor became uneasy and informed the health authorities. By this time only one decomposed carcase of a rat was available and, as was expected, the result of test with it was negative. Nevertheless there seems little doubt on the evidence that the epizootic, occurring as it did in one of the oldest centres of plague, was itself one of plague. *W. F. H.*

LIPATOVA (T.). **Immunological Studies on Plague. III. Thermo-precipitin Test and Elaboration of the Method of obtaining Specific Precipitating Plague Sera.**—*Rev. Microbiol., Epidémiol. et Parasit.* 1934. Vol. 13. No. 3. [In Russian pp. 201–206. [13 refs.] English summary p. 206.]

The anti-plague serum obtained by immunization of horses with the live cultures of *Past. pestis* produces a group precipitation with *Bact. coli, Past. pseudotuberculosis rodentium, Proteus, Bact. paratyphosum A, Bact. paratyphosum B,* which accounts for the precipitation by anti-plague serum of thermo-extracts from the organs of animals which died from causes other than plague. Saturation of the anti-plague serum with the thermo-extracts of all the above-named organisms removes from it the group antibodies for these bacilli. If the anti-plague serum is saturated with one of the filtrates it is thereby freed of the group antibodies homologous to all the organisms used in the experiment. On account of the close serological affinity between *Past. pestis* and *Past. pseudotuberculosis rodentium,* the latter should not be employed for saturation, especially since saturation with the thermo-extract of *Bact. coli* destroys the antibodies for *Proteus* and causes a marked diminution in the antibodies for *Past. pseudotuberculosis rodentium.*

The sera exhausted by one or several filtrates produce precipitation with the thermo-extracts from the corpses of animals experimentally infected with plague, but not with those from the corpses of non-infected animals. *C. A. Hoare.*

Minerwin (S. M.), Stupnitzki (P. N.) & Tinker (J. S.). Die Antipestvakzinen A-D. [**The Plague Vaccines A-D.**]—*Zent. f. Bakt.* I. Abt. Orig. 1935. Jan. 15. Vol. 133. No. 3/4. pp. 170–175.

Six types of vaccine were used in these trials and two species of animals, the ziesel mouse and the guineapig. The types were (1) dead and attenuated living, (2) salt and sugar bacterial suspensions, (3) virulent and avirulent plague organismal vaccines. Naturally only the avirulent strain was used for those vaccines in which the organisms were still living. A strain called No. 630 supplied the virulent and one called AMP the avirulent organisms. The special solution for sugar-suspension vaccines contained 150 parts of saccharose to 100 parts by weight of distilled water. A marked difference in the efficacy of the different types of vaccine was manifest, which was more or less the same for the two species of animals used. The results, expressed as percentage mortalities in ziesel mice, were for AMP salt, AMP sugar, AMP living, No. 630 salt, No. 630 sugar, and controls 57, 18, 18, 62·5, 25·5 and 75 respectively and the numbers of animals used in each category 14, 11, 11, 8, 12, and 12 respectively. Thus the sugar vaccines consisting of dead organisms and the attenuated living vaccine gave much the best results. *W. F. H.*

Albornoz (Francisco). Importancia de la desratización permanente y el saneamiento en la profilaxis de la peste bubónica. [**Importance of Permanent Deratization and Sanitation in the Prophylaxis of Plague.**]—*Rev. Inst. Bacteriológ.* Buenos Aires. 1934. July. Vol. 6. No. 3. pp. 304–329. With 35 figs. & 1 chart.

The port of Rosario, says the author of this article, has the distinction, if it may be called so, of having been the first place in which plague manifested itself in the Argentine. No case of the disease had occurred up to 1899. A vigorous campaign has been initiated in the last few years, of which the special features have been :—(1) Permanent deratization ; (2) Employment of a specialized personnel ; (3) Fixation of the personnel in each locality instead of the use of a flying squad ; (4) Practice of an intense and permanent sanitation. Numerous illustrations are given of the methods used and the obstacles which had to be overcome. A most instructive graph of morbidity and mortality concludes the article and, with its testimony to the plague condition prevailing from the years 1927 to 1930 and the reduction of both these characters practically to zero during the years 1930 to 1934, is eloquent of the effect which may reasonably be supposed to have resulted from the measures adopted. *W. F. H.*

Deprat. Peste bubonique et dératisation. [**Bubonic Plague and Deratization.**]—*Ann. d'Hyg. Pub., Indust. et Sociale.* 1935. Feb. Vol. 13. No. 2. pp. 78–100.

The author, who has had a long experience of plague from 1902 to 1927, both in practice and as port health officer of Rio Grande, here

expounds his views on the value of deratization as an anti-plague measure and questions current beliefs.

From the scientific investigations set on foot by the outbreak of plague at Hongkong in 1896 there has grown up the established doctrine that a rat epizootic is antecedent to the human epidemic and that transmission from the rat to man is effected by the agency of the flea. This doctrine has become the keystone of the arch of international sanitary defence against the scourge of plague. Deratization has been preached for 30 years as the sanitary safeguard against plague and as a specific international defence. But one may at the present time question whether this has not been a premature generalization on the experimental evidence of the possible transmission of plague from rat to rat by the flea. The demonstration of the transmission has not been made for the case of rat to man. This argument is developed throughout the article by the abundant citation of examples minimizing or negativing the evidence of the major part played by the rat and its fleas in transmission of plague to man. The foundations of the supposition are regarded as insufficient or at least as not excluding other means of propagation. Constant new importation of plague from the Argentine to Rio Grande and particularly through the agency of grain, without its ever becoming endemic and quite independent of any measure of sanitary defence, is one of the negative instances insisted on by the author out of his own experience. His conclusions stress the point of our ignorance upon essential points concerning the epidemiology, the prevention and the treatment of plague.

W. F. H.

Girard (G.) & Robic (J.). Vaccination contre la peste au moyen d'une souche de bacilles de Yersin vivants, de virulence atténuée.—*Ann. de Méd. et de Pharm. Colon.* 1934. July–Aug.–Sept. Vol. 32. No. 3. pp. 285–292.

Hussein (Abdel Gawad). Bubonic Anthrax simulating Plague.—*Jl. Egyptian Public Health Assoc.* 1934. 9th Year. Oct. pp. 25–26.

Khambatta (Kershaw D.). Plague in Poona City in 1933.—*Bombay Med. Jl.* 1934. July. Vol. 3. No. 7. pp. 189–191.

Urabe (K.). Species and Distribution of Mice in Mukden and Hwai-te. Studies of Animals connected with the Carrying of Plague. (Part I.)—*Jl. Oriental Med.* 1934. Sept. Vol. 21. No. 3. [In Japanese pp. 303–320. With 10 figs. on 2 plates. [22 refs.] English summary pp. 25–26.]

Uriarte (Leopoldo) with the co-operation of Blanca Calcagno, Marcos Riesel & Benjamin Anchezar. Pulicidés murins de Buenos Aires.—*Folia Biol.* Buenos Aires. 1934. June, July & Aug. Nos. 39–40–41. pp. 179–180. [A French summary of the paper noticed on p. 447 above.]

Uriarte (Leopoldo). Acerca de la peste bubónica en la Argentina.—*Rev. Inst. Bacteriológ.* Buenos Aires. 1934. Nov. Vol. 6. No. 4. pp. 446–457.

CHOLERA.

DOORENBOS (W.) Etude sur le vibrion cholérique. Vibrio cholerae typus épidémicus et Vibrio cholerae typus endémicus. [**The Cholera Vibrio. Epidemic and Endemic Types.**]—120 pp. 1934. Alexandrie : Société de Publications Egyptiennes.

There is no want of clarity in the views held and expressed by the author. He maintains that most if not all of the variants of the cholera vibrio, denominated para- or pseudo- cholera, are simply cholera vibrios. There is a definite epidemic cholera vibrio which, however, has no long existence in an epidemic before it ceases to maintain its peculiar serial cholerigenic character and becomes a " modified " vibrio. There is no such individual as a chronic carrier of the epidemic cholera vibrio but there are carriers of the modified cholera vibrio. These latter vibrios may be cholerigenic but not in series. They may account for sporadic cases.

In this way the author leads up to his classification of cholerigenic vibrios into the two great classes, the epidemic and the endemic. The modified cholera vibrio does not possess all the characters of the epidemic vibrio. It may or may not be agglutinable ; it may be haemolytic ; it may be otherwise modified. The agent which is most potent in modifying the epidemic cholera vibrio is the bacteriophage. It is by the action of bacteriophage that epidemics come to an end and the epidemic vibrio comes to its modified avirulent form. These views have a most important bearing upon the epidemiology of cholera especially on the meaning to be attached to the phrasing used in art. 29 of the International Convention of 1926 ; " Cases presenting the clinical symptoms of cholera . . . in which vibrios without the characters of the cholera vibrio have been found must be subjected to all the measures laid down for cholera." The same importance attaches to art. 101 of the new regulations adopted in 1934 by the Conseil Sanitaire Maritime et Quarantenaire of Egypt which couples together for quarantine purposes the " vibrion cholerique " and the " vibrion suspect," until the bacteriologist has pronounced the latter not to be a cholera vibrio. This pronouncement ought to be exact and furnished as rapidly as possible.

The memoir of the author is concerned with the two types of vibrio, the virulent epidemic type and the avirulent endemic type. It is not possible briefly to summarize the argument but some of the salient points may be touched on.

Quarantine for cholera is a disagreeable necessity for pilgrims and travellers. This was made especially prominent by the action of the sanitary authorities in Syria who examined very carefully travellers from Iraq at the time when Iraq was in the throes of an epidemic. This resulted at the beginning in the discovery of some 30 per cent. of carriers of vibrios, 12 per cent. of whom were carriers of true cholera vibrios. A great deal of research into the question of the cholera carrier has been made at the quarantine camp of Tor and controversy regarding the nature of the El Tor vibrio continues almost as vigorously to-day as it did after its first discovery in 1905. Transformation of vibrios, as will have been gathered from the opening summary, makes

up a good deal of the text in this monograph. We find that the author has seen agglutinating El Tor vibrios lose their agglutinability and vibrios which did not agglutinate become agglutinating El Tor vibrios. This famous vibrio is relegated to the category of a modified avirulent cholera vibrio. Much unanimity exists at the present day on the importance of agglutinability in the identification of the cholera vibrio, and yet we are told not to forget that " the choice of the agglutinating vibrio as the only true cholera vibrio " was in the first instance " an arbitrary choice and that the consequences of that choice are imposed upon us up to the present day."

Although D'HERELLE was the first to observe that cholera vibrios could undergo important modifications under the action of bacteriophage, the present author considers that he went beyond his facts in postulating that this modification was irreversible. One of the difficulties of such an association was to account for the preservation of the vibrio in nature. " It is more logical to admit that the cholera vibrio does not exist in nature in its ultra-pure and stable form but as a modified form which is more or less resistant to the bacteriophage and which can reacquire its original characters and its virulence when external conditions are favourable." This leaves the portal open, so to speak, for a return to biochemical, biological, cholerigenic and still further to epidemic characters. The characters of the epidemic or ultrapure strain are that it shows no gross contamination with bacteriophage, possesses a uniformity and regularity of biological characters and is homogeneous and stable. Cholerigenic power is dependent upon enterotropic character and this character is developed in high degree in the epidemic cholera vibrio. The endemic cholera virus is preserved in chronic carriers and is the ultimate source of recurrent epidemics, for the epidemic vibrio, although it is the homogeneous, stable, equilibrated form, cannot exist as such except for a very short space of time. Its epidemic existence is terminated by bacteriophage action and it returns once more to the dysequilibrated avirulent endemic type or state.

As the cholera carrier is the important personage from a quarantine point of view it is essential to know exactly how dangerous such carriers are and we have referred to the author's view that chronic carriers of the epidemic vibrio do not exist. We may add that the chronic carrier of endemic modified vibrios can give rise only to sporadic isolated cases of cholera ; it is the epidemic carriers in the stage of incubation of the disease who alone, as travellers and transmitters of virulent virus into an epidemic focus, present any really great danger to other populations. A final quotation would seem to put the question reasonably clearly although it is not a solution of the quarantine problem. " If we admit that the epidemic virulent vibrio does not lend itself to transport of a prolonged character and that the endemic vibrio, which does so, is usually avirulent, it is also necessary to admit that the carriers of vibrios are only dangerous for the propagation of cholera under very special conditions." We are left here presumably to the use of our own judgment as to the action which should be taken regarding carriers, but we are assured in conclusion that the sanitary measures applied to pilgrims during their stay at Tor and the systematic investigation of vibrio carriers offer sufficient guarantees for prevention of transportation of the virus of cholera into Egypt and into Europe.

W. F. Harvey.

Office International d'Hygiène Publique, Paris. **Report of the Cholera Commission to the Permanent Committee of the Office International d'Hygiène Publique. October Session 1934.** [M.S. copy received from the Ministry of Health, London.]

The first subject considered by the Commission was the preparation of a dried standard " O " cholera antigen for use in obtaining a high titre diagnostic serum. In such dried form the antigen could be despatched to all parts of the world and enable workers " to obtain exactly comparable serological results." The most suitable strain of the cholera vibrio to be used has still to be determined.

A very important decision was taken by the Commission with regard to the El Tor vibrio and haemolytic cholera-like vibrios generally. It amounted to a re-affirmation of the *status quo ante*, which is that these cholera-like vibrios even if they agglutinate with true cholera serum are not true cholera vibrios. This pronouncement has reference to a note presented by Dr. Doorenbos, the delegate for Egypt [see above]. It is set out briefly as follows :—

(*a*) The vibrios obtained from pilgrims at Tor are not considered to be true cholera vibrios, inasmuch as they may differ from that vibrio in haemolytic properties, bacteriophage resistance, etc., even if they possess certain serological characters of true cholerigenic vibrios. " It has not been shown," moreover, " that they are capable of producing cholera," nor does reversibility of characters prove identity.

(*b*) The separation of cholera vibrios into two types, with the nomenclature of *V. cholerae typus epidemicus* and *V. cholerae typus endemicus* and all its implications, is not advisable.

(*c*) Further evidence is required before acceptation of a specific source of contamination of pilgrims in the Hejaz. *W. F. H.*

Ghosh (H.). **Treatment of Cholera with a New Anti-Cholera Serum. Preliminary Note.**—*Brit. Med. Jl.* 1935. Jan. 12. pp. 56–57.

By anaerobic culture for 18 hours in special broth (this *Bulletin*, Vol. 30, p. 538) a toxic filtrate had been obtained which was capable of producing, by repeated small intravenous doses in rabbits, a cholera-like diarrhoea. Horses have been immunized with this toxin in doses as high as 500 cc. The serum obtained, when concentrated afforded an agglutinating titre of 1–12,000 " H " agglutinin and 1–1,600 " O " agglutinin. " A previous injection of serum prevented experimental production of cholera diarrhoea with the toxin in laboratory animals." Now the opportunity has occurred of testing the serum in human beings. By intravenous injection the serum did not prove entirely satisfactory except in mild cases of cholera. The author then adopted the intraperitoneal route of administration in a dose of 30 to 40 cc. serum, diluted with 200 cc. warm normal salt solution. A single saline transfusion was given on admission of a patient and then the serum. The results obtained in a limited series of cases were :—4 deaths in 32 treated with serum and 15 deaths in 57 cases treated without serum.

W. F. H.

Raynal (Jean). Etude des bactériophages appliqués à la prévention du choléra dans les Indes anglaises. [**Study of the Bacteriophages used for the Prevention of Cholera in British India.**]—*Rev. d'Hyg. et de Méd. Préventive.* 1934. Nov. Vol. 56. No. 9. pp. 669–690. With 2 figs. (1 map.)

This communication is the report of a mission specially detailed to "study in the bacteriological laboratory of Shillong in Assam the technique of preparation of bacteriophages and their practical application to the prevention of cholera." A large-scale experiment has been going on for some years now under Colonel Morison and his co-workers [see this *Bulletin,* Vol. 31, p. 891], which has attracted wide attention to the possibilities of phage in cholera and incidentally added to our knowledge of the action of phage. It is the striking result obtained in this trial and the evidence of what would appear to be a circumstantially controlled experiment which challenge and demand the verdict of all workers in preventive medicine. The French mission has not been content to read of these results but has journeyed to see them. In the article by the author we have set out, map, graph and table with full description of technique and a running commentary on what he heard and saw. An excerpt therefore from his final conclusion makes interesting, though somewhat disappointing, reading: "We are led therefore to conclude," says the writer, that "the whole question of anti-cholera bacteriophage, as well as the technique of its preparation are not yet definitely settled. It is difficult to be certain yet of the value of prophylactic methods for cholera founded upon the use of bacteriophage. . . . It is advisable still to await the result of the anticholera campaign with bacteriophage before passing judgment on its value. Nor is it at present desirable to replace the tried methods of prophylactic vaccination with anticholera bacteriophage. . . . Cholera is a disease in the presence of which one feels helpless. But the bacteriophage has given encouraging curative results. It would seem quite reasonable then to make a beginning with bacteriophage therapeutically. For this purpose it would be necessary to use bacteriophages which have been recently isolated at the time of an epidemic and which possess a high lytic activity on a large number of autochthonous cholera vibrios." *W. F. H.*

Morison (J.), Rice (E. Milford) & Haythornthwaite (R. A.). **Bacteriophage, Essential Oils and Vaccination and their Effects on Cholera Mortality.**—*Indian Jl. Med. Res.* 1934. Oct. Vol. 22. No. 2. pp. 317–339. With 3 graphs.

The argument developed in this article is in favour of the use of bacteriophage treatment of cholera as against vaccination of contacts and treatment of cases with essential oils. Two areas came under consideration, represented by parallel and adjacent valleys. Numerous tables and graphs are given of the data. The results are somewhat difficult to assess, in the absence of a summary of formal conclusions. *W. F. H.*

Raja (K. C. Kutty Ettan). **The Use of Bacteriophage against Cholera in North Arcot District, Madras Presidency, in 1933.**—*Indian Jl. Med. Res.* 1934. Oct. Vol. 22. No. 2. pp. 397–424.

A trial of bacteriophage has been instituted by the author from the Public Health Department of Madras. Some villages were taken as

controls and others selected for distribution of 'phage. In both groups, however, the usual methods for dealing with cholera were adopted including anti-cholera inoculation but in the test villages oral administration and addition to wells of 'phage were also carried out. Both the discussion and the conclusions make it appear that no satisfactory evidence was forthcoming for the efficiency of the 'phage used. We may, however, note the remark of the author that :—" It has to be emphasized that the figures dealt with in this report are small and that, therefore, it is unsafe to draw definite conclusions." *W. F. H.*

DAMBOVICEANU (A.) & SORU (E.). Action *in vitro* du bactériophage sur les propriétés des vibrions cholériques. [**Action of Bacteriophage *in Vitro* on Cholera Vibrios.**]—*C. R. Soc. Biol.* 1934. Vol. 117. No. 29. pp. 295–297.

Much attention is at present being devoted to the antigenic complexity of micro-organisms and especially of the cholera vibrios. The authors have investigated the changes in antigenic constitution of vibrios acted on by phage and summarize their results as follows :—(1) All the true cholera vibrios, both the smooth forms and those which are primarily rough before the action of bacteriophage, furnish extracts rich in residual antigen. (2) Vibrios which, being originally smooth, have become rough under the action of bacteriophage *in vitro*, no longer give any residual antigen. (3) Mixtures of smooth and rough furnish, after action of bacteriophage, extracts which are extremely poor in residual antigen. (4) Lastly, if the vibrios have been long in possession of rough characters, whether this has been before or after the action of bacteriophage, they provide extracts very rich in residual antigen.

W. F. H.

LINTON (Richard W.) & MITRA (B. N.). **Studies on the Antigenic Structure of *Vibrio cholerae*. Part VII. Two Acid-Soluble Protein Fractions.**—*Indian Jl. Med. Res.* 1934. Oct. Vol. 22. No. 2. pp. 295–308.

In the last of these studies [this *Bulletin*, Vol. 31, p. 893] the protein composition of cholera and cholera-like vibrios was studied and two proteins, I and II, found to be present. In this continuation study two acid-soluble protein substances, " A " and " B," have been isolated from cholera, cholera-like, smooth, smooth-rough and rough vibrios. " A comparison of all the chemical findings indicates that the ' A ' substance is very similar from whatever type of strain or protein it is extracted. ' B ' substance differs markedly from ' A,' but again is the same irrespective of source." " B " appears to be closely allied to residual protein after acid extraction and also to " whole protein." *W. F. H.*

GARDNER (A. D.) & VENKATRAMAN (K. V.). **The Antigens of *Vibrio cholerae*.**—*Lancet.* 1935. Feb. 2. p. 265.

A large group of vibrios exists with the same cultural and biochemical reactions as the *Vibrio cholerae* and the same heat-labile or H. antigen. This group is capable of subdivision on the basis of differences in heat-stable or O antigens. Agglutination and absorption tests with O sera are largely used for differentiation. A condensed preliminary account is here given of an examination of the Japanese subdivision into their

original, middle and variant types, with confirmation of the reality of the first and third. The table published shows that "the Japanese type differences are in no way confined to Japanese vibrios. Races from India, China and elsewhere show the same variations of their subsidiary O antigens and even among the haemolytic vibrios from El Tor (Dr. Doorenbos) those that fall into the same O subgroup as the classical cholera vibrio (by no means all of them do so) show the same kind of variation." *W. F. H.*

UYEDA (Saburo). **Local Skin Reactivity to the Culture Filtrate of *Vibrio cholerae* as demonstrated by Shwartzman Phenomenon.**—*Acta Scholae Med. Univ. Imperialis in Kioto.* 1934. Vol. 17. No. 2. pp. 146–158. With 3 figs. on 1 plate. [15 refs.]

According to SHWARTZMAN if rabbits which had been injected intracutaneously with a filtrate of *Bact. typhosum* received 24 hours later an intravenous injection of the same filtrate, there developed at the site of the previous injection a severe haemorrhagic necrosis. Later work showed that the necrosis could be produced by filtrates of other than the specific organism. The phenomenon was therefore not strictly specific. The author has used filtrates of *V. cholerae*, produced the phenomenon and again found it to be non-specific. *W. F. H.*

LINTON (Richard W.), SHRIVASTAVA (D. L.) & MITRA (B. N.). Notes on the Structure of the Cholera and Cholera-like Vibrios.—*Indian Jl. Med. Res.* 1934. Oct. Vol. 22. No. 2. pp. 309–312.

REVIEWS AND NOTICES.

Ioff (I. G.). **[Memorandum on Anti-Malarial Campaign in Collective and Soviet Farms.]**—104 pp. With 6 text figs. (In Russian.) 1934. Rostoff-on-Don: Published by the Azov-Black Sea Regional Tropical Institute. [Price 50 kopecks.]

This small book is intended to serve as a practical guide for "bonificators" or sanitary inspectors in charge of anti-malaria measures in the state-managed (Collective and Soviet) farms. It provides the necessary elementary information regarding the bionomics of the mosquitoes, the methods of their destruction and the methods of protecting human dwellings from them. A brief account is also given of the treatment and prophylaxis of malaria. *C. A. Hoare.*

Logie (H. B.) [M.D., C.M., Executive Secretary]. [Edited by.] **Standard Classified Nomenclature of Disease. Compiled by the National Conference on Nomenclature of Disease.** [2nd Edition.]—pp. xxi+870. 1935. New York: The Commonwealth Fund. [15s.]

This book was first issued less than two years ago; the second edition contains 170 more pages than the first, but the book is not materially increased in size and the price has been reduced. The preface affirms that the work has been well taken up in America and has found its way into nearly 500 hospitals in the United States and Canada. By retaining communication with those working at these hospitals the authors have been able to avail themselves of the experience gained and use it in preparing the present edition. The same general plan has been followed, but changes have had to be introduced in all sections and two have had to be re-written. It attempts to include any morbid condition clinically recognizable.

The work must have entailed a vast amount of labour and only time and experience can tell whether the results will be commensurate. Many will not be inclined to agree that it will prove labour-saving, as the reviewer's experience may demonstrate. The user is directed to "read the introduction and consult the index" before setting out to designate the disease by numbers. Probably considerable practice and more thorough knowledge of the rules of the game are needed. Following directions, the reviewer looked out Sprue, and found it given in the index as 113 (7). The number in brackets we are told "refers to the etiological category" *i.e.*, metabolism, growth or nutrition. So far so good. Page 113 gives "sprue" and against it 010–703. Now 010 appears (p. 106) to stand for "Body generally" (somewhat arbitrarily, perhaps). To track down 703 we turn to the "etiological category" and find on p. 82, that 70 is "disturbance of general nutrition" and 703 "deprivation of a particular kind of food." How far this is a true interpretation of sprue is a matter of opinion which will vary according to the views of the physician treating the patient. After trying to trace other tropical conditions we found the game quite absorbing and more than once had to leave the problem unsolved feeling that as a winter evening's employment it is every bit as intriguing and perhaps as instructive as the average crossword puzzle. We were, however, convinced that it would be quickly and more readily comprehended to enter the diagnosis as Sprue (*tout court*) and place the

card in the S. section. As was stated in the review of the first edition [see this *Bulletin*, Vol. 30, p. 329] : " In this country [Great Britain], however, and throughout the British Empire, the Nomenclature of Diseases [Royal College of Physicians] must continue to form the basis of all official records for the present," and until the methods of this work under review are much simplified we feel that it is better so.

H. H. S.

MAJUMDAR (Akhil Ranjan) [M.B., Bengal Medical Service, etc.]. **Bed-Side Medicine. A Hand-Book of Medical Diagnosis, Symptoms, Physical Signs and Laboratory Methods, from Tropical Standpoint.** Third Edition.—pp. xii + 815. With 248 figs. 1934. Calcutta: The Book Company, Ltd. 4/4a College Square. [8 rupees.]

A book that has reached a third edition within about six years of the publication of the first has surely proved its utility and popularity. Dr. A. R. Majumdar's " Bedside Medicine " differs from the usual book on clinical diagnosis by the larger amount of space given to tropical diseases, and it is a great advantage to see the symptoms of these set out side by side with those of the diseases of cosmopolitan distribution.

The book has been considerably enlarged since the second edition was reviewed in this *Bulletin* (1931, Vol. 28, p. 336), and new diagrams and illustrations have been added, but it still remains of a convenient size.

After describing the procedure for the routine examination of a patient—with, incidentally, a sound caution against the temptations of a " lightning diagnosis "—the author contrasts the different kinds of fevers, and then goes on to a detailed account of the derangements of the various systems of the body. All these sections are very complete ; that on the nervous system is particularly lucid. Wherever the book has been tested, it has been found to be reliable and up to date in its information. It does not replace a good textbook, and it is not meant to do so ; but it will be a very useful aid to revision for students and practitioners. Quite apart from the large number of important facts of which he will be reminded, the student, who reads the book carefully and takes its method to heart, will have gone a long way towards the acquisition of an orderly mind, and will have learned to approach the very important subject of diagnosis in the only satisfactory way, which allows of no short cuts.

There are about 250 illustrations, most of which are quite adequate ; the book is strongly bound, and well printed in type of a reasonable size, and the price (eight rupees) is extremely moderate.

H. J. Walton.

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